

2. Patient 220-3256, 52 years old, had a diagnosis of MI 10 days following his last dose of Cialis 20 mg. He subsequently had successful angioplasty and was discontinued from study due to this AE.
3. Patient 817-8600, 58 years old, was admitted to hospital for the complaint of chest pain 2 days following his last dose of Cialis 20 mg. Cardiac work-up was normal, and the patient was diagnosed as having had esophageal spasm.
4. Patient 004-4087, 73 years old, was reported as having a stroke 4 weeks after his last dose of Cialis 10 mg. He was discontinued from the study, and is continuing recovery at home following 4 months at a rehabilitation facility.
5. Patient 408-1084, 69 years old, was reported as having a cerebral infarct and atrial fibrillation 29 days following his last dose of Cialis 20 mg. The subject had received a total of 84 doses of Cialis 20 mg during the 9 months prior to this event, and was discontinued from the study due to the fibrillation.

Reviewer's Comment: I concur with the investigators' opinions that in cases #1-4, the events were unrelated to study drug. However, I disagree with the investigator's opinion that the event in case #5 was possibly related to study drug, and concur with the Sponsor's assessment that the patient's underlying diseases, particularly the atrial fibrillation, and long interval between dose and event, leads to the conclusion that this AE was unrelated to study drug.

Reviewer's Comment: With reference to the 9 patients with serious AE's (including deaths) that were identified by the Division as having insufficient primary data; the reader should be aware that the Sexual Encounter Profile diaries remained lost despite reasonable attempts at recovery.

3.5.4. Comprehensive Case Summaries in Regard to Cardiovascular Events

Appendix 4 of the Complete Response consists of reports of 4 subjects with serious AE's, including death, recorded in the 2 months after the previous cutoff date, November 2, 2002. In all these cases, the investigator coded the event as unrelated to drug.

Reviewer's Comment: This reviewer concurs with the investigators' assessments that these events were unrelated to study drug.

Appendices 5-13 of the Complete Response consists of reports of all the clinically significant cardiovascular events from the clinical studies and the clin-pharm studies.

3.5.4.1. Clinical Pharmacology Trials and Cardiovascular Events

In clinical pharmacology trials, there were 12 reported events: MI/ischemia in 2 subjects, ventricular arrhythmia in 1 subject, and syncope/hypotension in 9 subjects, which the investigators regarded as unrelated to study drug.

Reviewer's Comment: This reviewer agrees with the investigators assessment in these cases.

3.5.4.1.2. Clinical Studies and Cardiovascular Events

The following Cardiovascular events were seen in the clinical studies.

- | | |
|-----------------------------|---|
| 1. Cardiac Arrest. | 4 cases. All listed as unrelated to study drug. |
| 2. Ventricular Arrhythmia. | 2 cases. All listed as unrelated to study drug. |
| 3. CHF. | 2 cases. All listed as unrelated to study drug. |
| 4. MI/Ischemia | 31 cases listed as unrelated to study drug, 1 case listed as related to study drug, and 5 cases listed as possibly related to study drug. |
| 5. Cerebrovascular events. | 10 cases listed as unrelated to study drug, and 1 case listed as possibly related to study drug. |
| 6. Syncope/Hypotension | 8 cases listed as unrelated to study drug and 2 cases listed as possibly related to study drug. |
| 7. Supraventric. Arrhythmia | 3 cases. All listed as unrelated to study drug. |
| 8. Other arrhythmias | 1 case. All listed as unrelated to study drug. |
| 9. Pulm. Embolism | 1 case. All listed as unrelated to study drug. |

Reviewer's Comments: Upon review of the case summaries of these events (see full list below), this reviewer does not concur with the assessments of possible study drug relatedness in 14 of the MI/Ischemia events, 8 of the Syncope/Hypotension events, and 4 of the cardiovascular events. The subject numbers for these cases are listed below. In these patients, this reviewer believes that despite underlying cardiovascular risk factors cited in many of these cases, the events are possibly related to study drug.

Case summaries list:

MI/Ischemia. Patient numbers 002-0126, 002-4017, 003-4062, 007-0232, 009-0279, 018-4319, 602-6067, 500-5048, 316-6699, 341-6103, 604-6337, 610-6511, 401-4412, 817-8600.

Syncope/Hypotension. Patient numbers 01-004, 01-006, 01-014, 02-040, 012-3322 (12013), 010-3454, 018-1851, 504-5244.

Cardiovascular. Patient numbers 208-3121, 411-1113, 411-1129, 313-3657.

3.5.5. Study LVBZ:

Title: "Evaluation of the Effects of Cialis on Myocardial Perfusion using PET Scans."

This was a single-institution study conducted by 1 investigator involving 7 subjects, ages 52-73, with CAD. This study was designed to:

1. Assess the safety, tolerability, and effects of a single dose of Cialis 20 mg, compared with placebo, on global and regional myocardial blood flow in patients with CAD, both at rest and after pharmacologic stress with dobutamine and with adenosine.
2. To compare its effects, compared with placebo, on cardiac wall motion in patients with CAD.

Reviewer's Comments: The small sample size limits this to an observational study.

3.5.5.1. Results of LVBZ

Global Myocardial Blood Flow: Baseline blood flow was similar for both Cialis and placebo. Following adenosine, there were similar increases in blood flow for Cialis (1.09 mL/g/min) and placebo (1.16 mL/g/min). Dobutamine also induced similar increases in blood flow for Cialis (0.88 mL/g/min) and placebo (0.71 mL/g/min).

Regional Myocardial Blood Flow: For each region, baseline blood flow was generally similar for Cialis and placebo. Following adenosine, there were similar increases for Cialis and placebo. Following dobutamine, there was a trend (in 8 of the 9 regions) for a greater increase for Cialis over placebo, and a statistically significant increase only in the distal lateral region.

Cardiac Wall Motion: For both Cialis and placebo, and all regions, wall motion for most subjects were hypokinetic, normal or hyperkinetic at baseline, post-adenosine and post-dobutamine. For adenosine and dobutamine, a similar number of Cialis and placebo subjects had a change from baseline of 1 or more (excluding 1 change from 1 to 2).

Safety and Tolerability: There were no deaths or serious AE's. The majority of AE's were regarded as being related to adenosine or dobutamine, and no events were considered related to study drug or placebo.

Sponsor's Conclusions Regarding LVBZ: For a single dose of Cialis 20 mg in subjects with CAD:

1. The drug is safe and well tolerated.
2. There is no apparent effect on global or regional myocardial blood flow in subjects at rest.
3. The dobutamine-induced increase in global myocardial blood flow did not differ between Cialis and placebo.
4. The dobutamine-induced increase in regional myocardial blood flow did not differ for 8 of 9 regions. However, there was a trend toward an increase in most regions with Cialis, and a statistically significant increase in the distal lateral region.
5. Adenosine caused an increase in both global and regional blood flow, significantly greater than that for Cialis alone, which was similar to placebo.
6. There was no apparent effect on cardiac wall motion either at rest or during administration of adenosine or dobutamine.

Reviewer's comment: The reviewer concurs with sponsor's conclusions.

3.5.6. Study LVCP:

Title : "Evaluation of Cialis During Exercise Stress Testing in Subjects with CAD."

Twenty-three subjects (ages 53-75) entered and completed the study conducted by 2 investigators at 2 institutions. This study was designed to evaluate:

1. The effect of Cialis 10 mg on the time to ischemia, in patients with CAD, during exercise stress testing
2. The hemodynamic effects of sublingual nitroglycerine, in the presence of Cialis 10 mg as a single dose, in male or female subjects with CAD, after the onset of exercise-induced ischemia.

Reviewer's Comments:

1. It would have been more clinically meaningful if the dose selected for Cialis was 20 mg (the maximum dose proposed for marketing) rather than the 10 mg dose.
2. The small sample size limits conclusions that may be drawn from this observational study.

3.5.6.1. Results of Study LVCP

The following tables show the time to ischemia and post-dose changes in hemodynamics, respectively.

Table 12: Study LVCP; Summary of Total Exercise Time/Time to Ischemia (minutes:seconds)

	Total exercise time/time to ischaemia (minutes:seconds)	
	10 mg IC351 & 0.4 mg SL-NTG (N=23)	Placebo & 0.4 mg SL-NTG (N=23)
Mean (SD)	13:36 (1:59)	13:31 (2:08)
Minimum	9:19	9:12
Maximum	16:36	17:15

Table 13: Study LVCP; Summary of Clinically Significant Changes in BP after Post-Exercise Doses of Cialis & NTG.

Criteria	10 mg IC351 & 0.4 mg SL-NTG (N=23)	Placebo & 0.4 mg SL-NTG (N=23)
Sitting systolic blood pressure <85 mmHg	7 (30%)	1 (4%)
Sitting diastolic blood pressure <45 mmHg	1 (4%)	0 (0%)
Change from baseline in sitting SBP >30 mmHg	21 (91%)	23 (100%)
Change from baseline in sitting DBP >20 mmHg	8 (35%)	5 (22%)

Safety and Tolerability: There were no deaths or serious AE's. The number of subjects with adverse events considered to be related to drug or placebo were 5 (21.7%) and 3 (13%), respectively. All AE's were mild or moderate, and the most common AE seen with Cialis was headache, with single episodes reported by 3 subjects. Only 1 subject reported more than 1 AE for each treatment.

Sponsor's Conclusions Regarding LVCP

1. There was no evidence that Cialis significantly reduces the time to ischemia in this trial.
2. After the onset of exercise-induced ischemia, more subjects experienced lower SBP following NTG in the presence of Cialis, than in the presence of placebo. This is an expected consequence of the well-known PDE5 inhibitor-nitrate interaction.

3.5.7. Conclusions and Recommendations Regarding Cardiovascular Events

Conclusions

1. The sponsor's Complete Response and supplementary information has satisfied the Division's concerns regarding cardiovascular AE's which had not been adequately explored in the NDA submission; namely: a) A full characterization and analysis of the cardiovascular AE's reported in the NDA that address any potential relationship to Cialis. b) Information addressing insufficient diary or other primary data in some patients experiencing serious AE's. c) Results from

Study LVBZ (coronary blood flow) d) Results from Study LVCP (exercise tolerance in men with stable CAD).

2. The information provided supports the conclusion that with reference to cardiovascular AE's, Cialis is not associated with an increased incidence of potentially clinically significant events.
3. A review of the comprehensive case summaries and supplementary material failed to reveal new significant findings.
4. A review of Studies LVBZ and LVCP supported the conclusions that in subjects with CAD, Cialis had no adverse effect on myocardial blood flow either at rest or during pharmacologic stress with dobutamine, and does not reduce time to myocardial ischemia during exercise stress testing.

Overall assessment of the response:

1. The sponsor has adequately explored the cardiovascular adverse events in association with Cialis administration. The study reports from the studies LVBZ and LVCP support the view that Cialis had no adverse effect on myocardial blood flow either at rest or during exercise stress testing.
2. The label should include the following paragraph in the clinical pharmacology section: "Effects of Cialis on Exercise Stress Testing: The effects of Cialis on cardiac function, hemodynamics and exercise tolerance were investigated in a single clinical study. In this blinded crossover trial, twenty-three patients with stable coronary artery disease and evidence of exercise-induced cardiac ischemia were enrolled. The primary endpoint was time to cardiac ischemia. The mean difference in total exercise time between CIALIS 10 mg and placebo was 3 seconds, which represented no clinically meaningful difference. Further statistical analysis demonstrated that CIALIS was non-inferior to placebo with respect to time to ischemia. Of note, in this study, in some patients who received CIALIS followed by sublingual nitroglycerin in the post-exercise period, clinically significant reductions in blood pressure were observed."

3.6. Drug-Drug Interactions:

Clinical Deficiency #2 under other additional recommendations states:

“Provide information to support labeling regarding interactions of 20 mg Cialis with the following: ketoconazole 400 mg, ritonavir, doxazosin, or terazosin (in doses used for symptoms of benign prostatic hypertrophy), other relevant antihypertensive medications, warfarin, and aspirin.”

The reader is referred to the clinical pharmacology review by Drs Kenna and Jarugula in regard to drug-drug interaction studies between Cialis and ketoconazole, ritonavir and doxazosin. The review of studies LVEX and LVEY is presented below.

3.6.1. Interactions with Warfarin (Study LVEX)

Study LVEX was performed to address the warfarin deficiency in the approvable letter. This study was a randomized, double blind, placebo-controlled, crossover study assessing the effects of coadministration of 20 mg tadalafil on the pharmacokinetics and pharmacodynamics of warfarin (25-mg single dose)

A total of 16 healthy male subjects aged between 18 and 60 years entered the study and 12 subjects completed the study. Subjects #4 (placebo), #6 (Cialis), #9 (placebo) and #12 (Cialis) were withdrawn from the study in Treatment Period 1 due to a prothrombin time of less than 50% at discharge from the Unit (48 hours after dosing) and they were given Vitamin K. These subjects were replaced by Subjects #104, #106, #109 and #112 who all completed the study.

Study LVEX Results:

1. Pharmacokinetics:

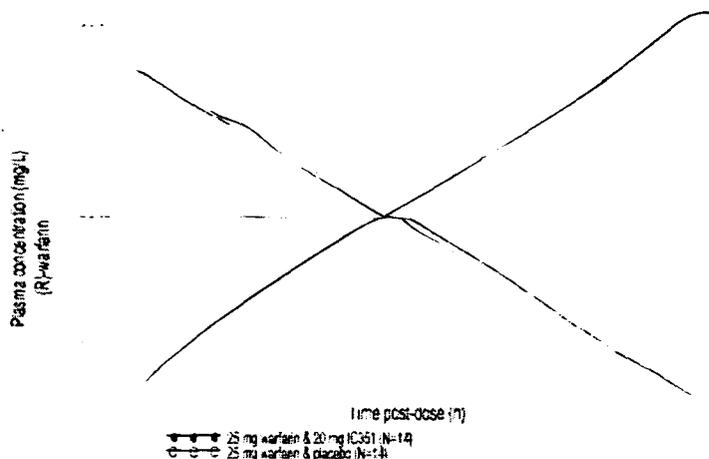
For both (R)- and (S)-warfarin, the mean plasma concentration-time profiles were similar in the presence of steady-state concentrations of IC351 or after multiple dosing of placebo. The mean exposure to warfarin showed a small reduction (<10%) with co-

administration of 20 mg tadalafil. Plasma (R)- and (S)-warfarin concentrations were quantifiable at 0.5 hours post-dose for all subjects following co-administration of warfarin with IC351 or placebo. Individual values for C_{max} were very similar for (R)- and (S)-warfarin, and ranged from [redacted] for (R)- and (S)-warfarin, respectively, following co-administration of warfarin with IC351, and from [redacted] for (R)- and (S)-warfarin, respectively, following co-administration of warfarin with placebo.

Individual t_{max} values following co-administration of warfarin with IC351 ranged from 0.5 to 2 hours for both (R)- and (S)-warfarin. Following administration of warfarin with placebo, t_{max} ranged from 0.5 to 4 hours for both for (R)- and (S)-warfarin.

The figure below shows R-warfarin time concentration curve. The figure for S-warfarin is similar.

Figure 1. Warfarin Concentration Curve.



2. Pharmacodynamics:

Prothrombin time (%) decreased following co-administration of warfarin with IC351 or placebo. From the statistical analysis, mean prothrombin time (%) reached minimum values of 53% (placebo) and 54% (IC351) at 36 hours post-dose for both treatments. The mean maximum change in prothrombin (PT) and AUC for the change in PT versus time curve were not different between tadalafil and placebo.

Reviewer's Comments:

These results are similar to a previous Cialis-Warfarin interaction study (LVAQ) using 10mg of Cialis. I agree with the sponsor's conclusion that there is a clinically insignificant interaction between Warfarin and Cialis. In this study Cialis did not significantly add to the warfarin-induced prolongation of prothrombin time.

3.6.2. Interactions with Aspirin (Study LVEY)

Study LVEY was performed to address the aspirin deficiency in the approvable letter. This study was a randomized, double blind, placebo-controlled, parallel study comparing the effect of 20 mg tadalafil on aspirin-induced prolongation of bleeding time compared to placebo.

Twenty-nine healthy male subjects, aged between 18 and 60 years entered the study and 28 completed. In this study, aspirin (300 mg) was administered to all subjects for 5 consecutive days. On the fifth day, tadalafil or placebo were co-administered with aspirin. Bleeding times were assessed pre-dose and post-dose on Day 5. Bleeding times in both groups were longer following post-dose than pre-dose. There was no difference in the bleeding times either pre-dose (pre-aspirin on Day 1 as well as pre-tadalafil/placebo on Day 5) or post-dose.

3.6.2.1. Study LVEY Results:

Pharmacodynamic Evaluation

Mean bleeding time was increased for both treatment groups, following once-daily oral dosing with aspirin (300 mg) over 4 consecutive days. The increase in bleeding time was similar for both treatments, with the ratios of the means for Day 5 (predose) to Day 1 (pre-dose) being 1.45 and 1.52 for the placebo and IC351 groups, respectively.

Reviewer's comments:

These findings are consistent with a previous Cialis-aspirin interaction study (LVBV) assessing the effect of 10 mg tadalafil on aspirin-induced prolongation of

bleeding time. This reviewer agrees with the sponsor's conclusion that there is no potentiation of aspirin-induced prolongation of bleeding time following a single oral administration of 20 mg tadalafil.

Overall assessment of the response:

The sponsor has adequately explored various drug-drug interactions stated in the approvable letter. Please see clinical pharmacology review for the details of the Cialis – alpha-blocker interaction studies.

Labeling recommendations:

1. Aspirin: Tadalafil did not potentiate the increase in bleeding time caused by aspirin. However the patients with bleeding disorders and the patients with peptic ulceration were not studied and therefore there should be notation to this affect.
2. Warfarin: Tadalafil did not have a clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin, nor did tadalafil affect changes in prothrombin time induced by warfarin.
3. Alpha-blockers: (also see the Clinical Pharmacology review)
 - Administration of CIALIS to patients taking any alpha-adrenergic antagonist other than tamsulosin 0.4 mg once-daily is contraindicated.
 - In a drug-drug interaction study, when tadalafil 20 mg was administered to healthy subjects taking doxazosin (8 mg daily), there was a significant augmentation of the blood-pressure-lowering effect of doxazosin.
 - Safe use of Cialis with alpha-blockers other than tamsulosin 0.4 mg daily has not been demonstrated.

3.7. Visual Effects

Clinical Deficiency #3 under other additional recommendations states:

“Provide data for labeling on quantitative effects of Cialis on color vision and retinal physiology (as measured by ERG testing). Testing after repeat dosing of Cialis 20 mg must be performed.”

Background:

Phosphodiesterase inhibitors have the potential to affect visual function. The mechanism is believed to involve the inhibition of PDE6, an enzyme found in the retina and thought to be responsible for phototransduction. The administration of Viagra (sildenafil tablets) has demonstrated dose-dependent changes in visual perception and changes in Farnsworth-Munsell 100 hue testing and ERG testing. Clinical studies LVAN and LVCN were reviewed by Dr. Wiley Chambers. He also provided guidance to the sponsor regarding the protocol for Study LVFF.

Sponsor's Response**Study LVFF:**

This study was a single center, double-blind, randomized, placebo-controlled, 3-period cross-over study performed on healthy male subjects (18-45 years of age). A total of 63 subjects entered and 59 subjects completed the study in accordance with the protocol, protocol amendment (a), and the treatment randomization. Subjects were dosed with 40 mg IC351, active comparator, or placebo on Day 1 in each treatment period, such that they received one dose of each of the three treatments.

The primary objective was to assess, the effects of 40 mg IC351 and active comparator after a single oral dose on color vision as determined by the FM-100 Hue test. Other assessments included ERG, visual acuity, and visual fields

As with the previous studies LVAN and LVCN, Dr. Chambers held the view that study LVFF was flawed. His comments on visual effect of Cialis included:

1. The FM was to have been tested for each eye separately. A binocular test was performed instead. This is a fatal flaw for this test. The results are therefore not interpretable.
2. The ERG is affected by IC351. The white light a-wave latency is lengthened.
3. There is no significant difference in visual acuity between groups (Placebo, comparator and Cialis).

4. No change in the characteristics of adverse ocular events in the safety update.
5. Dr. Chambers' recommendation on approvability: "From an ophthalmologic prospective, there is no objection to the approval of this NDA provided that the labeling is consistent with other phosphodiesterase inhibitors. Specific changes to the originally proposed labeling have been identified in this review."
6. Dr. Chamber's recommendation on Phase 4 studies and risk management steps: "Additional adequate and well-controlled studies are recommended to better quantitative the effect of tadalafil on color vision and retinal physiology (as measured by ERG testing). In particular, testing after repeated dosing should be performed."
7. Dr. Chambers' proposed labeling recommendations:
 - Studies of CIALIS on Vision. Tadalafil is a phosphodiesterase inhibitor. Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green) using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in photo transduction in the retina. In a study to assess the effects of a single dose of tadalafil 40 mg on vision (N=59), no effects were observed on visual acuity, intraocular pressure, or pupillometry. Across all clinical studies with CIALIS, reports of changes in color vision were rare (<0.1% of patients).

•

•

Overall assessment of the response:

1. The sponsor submitted a flawed study to assess the effects of Cialis on vision (Study LVFF). Specifically, the color vision was tested binocularly and that procedure made the results of this study uninterpretable. No claims other than that of a class label can be allowed.
2. The following paragraph can be included in the label:

“Single oral doses of phosphodiesterase inhibitors have demonstrated transient dose-related impairment of color discrimination (blue/green) using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. In a study to assess the effects of a single dose of tadalafil 40 mg on vision (N=59), no effects were observed on visual acuity, intraocular pressure, or pupillometry. Across all clinical studies with CIALIS, reports of changes in color vision were rare (<0.1% of patients).”
3. A Phase 4 commitment to conduct an adequate, multiple-dose vision study has been obtained from sponsor..

3.8. Applicability of Clinical Trial Data to the US Population; Efficacy of Cialis in Patients With ED Status-Post Bilateral Nerve-Sparing Radical Prostatectomy; and Duration of Effectiveness of Cialis

Clinical Deficiency #5 under other “additional recommendations” states:

“Less than 1% of the clinical trial population (all performed outside the US) was of African origin and only 2 to 3% of Spanish origin. Provide information to show that results from these trials can be applied to the US population.”

Sponsor’s Response

The sponsor submitted new clinical study reports on 4 clinical trials that addressed the following issues:

1. *Studies LVCR and LVEF* - Applicability of previously submitted foreign data to US population.
2. *Study LVCI* - Efficacy of Cialis in Patients With ED Status-Post Bilateral Nerve-Sparing Radical Prostatectomy
3. *Study LVFD* - Duration of effectiveness of Cialis

These 4 studies are reviewed in the following sections.

3.8.1. US Trials (LVCR, LVEF):

The U.S. Phase 3 clinical studies LVCR and LVEF enrolled 402 subjects, 305 of them treated with tadalafil. Each study compared 20mg tadalafil with placebo taken “on demand”. Both studies were randomized, double-blind, placebo-controlled, parallel-design studies with a 3:1 randomization ratio (tadalafil:placebo). These studies included 13.7% African-Americans and 7.2% Hispanics.

The study design and patient selection was essentially the same as in the pivotal Phase 3 studies in the original NDA. The three co-primary endpoints in all of these studies were the Erectile Function Domain of the International Index of Erectile Function (IIEF) and Sexual Encounter Profile Questions 2 and 3 (SEP Q2 and SEP Q3).

3.8.1.1. Study LVEF:

This was a multicenter, randomized, double-blind, parallel, placebo-controlled study to evaluate the efficacy and safety of 20 mg tadalafil or placebo administered for 12 weeks to men with ED. After a 4-week treatment-free run-in period, approximately 210 subjects were stratified by IIEF Erectile Function Domain score as follows: mild ED = 17 through 30, moderate ED = 11 through 16, severe ED = 1 through 10. They were then randomly assigned within each severity group into treatment groups in a 1:3 (placebo: 20 mg tadalafil) fashion. This was followed by a treatment period that lasted 12 weeks.

Study population: The study groups were balanced. The mean age was 59 years for both treatment groups. A majority of subjects in both treatment groups were Caucasian: 36 (75.0%) and 115 (72.3%) in the placebo and tadalafil groups, respectively. Subjects of African descent numbered 4 (8.3%) in the placebo group and 22 (13.8%) in the tadalafil group, and Hispanic subjects numbered 7 (14.6%) in the placebo group and 19 (11.9%) in the tadalafil group.

Reviewer's comments: Trial design, conduct and population selected are acceptable to test efficacy and safety of Cialis in US population. The study groups are balanced.

Compliance, and protocol violations: In the study LVEF, 207 subjects were randomized (48 placebo, 159 tadalafil), and 31 of the randomized subjects were discontinued early. The majority of subjects (85.0%) completed this study. Of the 8 placebo subjects (16.7%) who discontinued the study, a majority (5, or 10.4% of all placebo subjects) discontinued due to a perceived lack of efficacy. Of the 23 tadalafil-treated subjects (14.5%) who discontinued the study, 3 (1.9%) discontinued due to a perceived lack of efficacy, 8 (5.0%) discontinued due to an adverse event, and 5 (3.1%) discontinued due to being lost to follow-up.

Reviewer's comments: Compliance issues and protocol violations did not impact on the outcome of the trial.

Efficacy analysis: The following table compares all three primary efficacy variables between the groups.

Table 14: Study LVEF; Summary of Primary Efficacy Variables All Randomized Subjects:

	All (N=207)	Placebo (N=48)		IC 20mg (N=159)		P
	BASELINE	END	CHG	END	CHG	
IIEF Domain - Erectile Function	13.3	13.6	0.3	22.5	9.3	<.001
Patient SEP Questions						
SEP2 - Insert Penis into Vagina	44.1	42.8	2.3	76.8	31.6	<.001
SEP3 - Successful Intercourse	20.3	22.6	3.5	64.2	43.6	<.001

Reviewer's assessment of efficacy: Tadalafil 20mg demonstrated a clinically meaningful and statistically significant improvement in the ED endpoints tested in this population. These results are similar to those seen in the previous pivotal studies.

Safety analysis:

Extent of exposure: This was an on-demand study in which subjects were given study drug to take on an as-needed basis for a period of 12 weeks. Subjects were to take one dose prior to expected sexual activity, and not to exceed one dose daily. Subjects were randomized to treatment as follows: 48 to placebo and 159 to 20 mg tadalafil. Exposure to study drug was similar between the treatment groups.

Deaths:

No deaths occurred after randomization. One patient died due to a massive cerebrovascular accident after Visit 1, before he was randomized.

Serious Adverse Events:

After randomization, 4 subjects experienced SAE's, all of which involved hospitalization. The narratives are as follows:

1. Subject 0327-4261 (tadalafil) had multiple cardiac risk factors (hypercholesterolemia, diabetes mellitus, and hypertension). On the morning of _____ the subject took a dose of study drug, which was followed by a sexual attempt approximately 30 minutes later. Later that same morning, he presented to his cardiologist with chest pain

that was different in character from his usual chest pain. He was evaluated in the Emergency Room and underwent cardiac catheterization. He was found to have a significant lesion of the circumflex artery and a stent was placed. He was discontinued from the study after he reported this event to the investigator. He did not report chest pain following any of his other doses in the study. The investigator considered the event possibly related to study drug.

2. Subject 0426-5305 (tadalafil) had a history of coronary artery disease since 2000 and angioplasty in the same year. He began taking study medication in January 2002 and took his last dose on the morning of 05 March 2002. The same evening, he had a sexual attempt and developed chest pain lasting a few seconds. He was evaluated and found to have severe three-vessel coronary artery disease and underwent coronary bypass surgery.

Reviewer's comment: These cases provide further evidence that nitrates may well be required during the post-dosing period with Cialis.

3. Subject 0415-5002, having been hospitalized for a carotid endarterectomy, was initially reported as experiencing an SAE. However, it was learned subsequently that the subject had been on a waiting list for surgery prior to entry and that his preexisting condition had not changed.

4. Subject 0401-4412 (tadalafil) had a history of intermittent right ankle pain. During the study, the subject underwent a tendon synovectomy 1 day following his last dose of study medication. Postoperatively, the subject experienced elevated blood pressure (276/117 mmHg) and chest pain.

Reviewer's Comments:

This reviewer agrees with sponsor that none of the SAE's described above can be definitively attributed to the drug.

Discontinuations due to adverse event:

Adverse events led to discontinuation of 8 subjects in the tadalafil group: 6 subjects with non-serious adverse events (headaches) and the 2 subjects with chest pain and coronary artery disease. Additionally, 1 subject in the placebo group discontinued due to headache.

Reviewer's Comments:

Headache is known to be related to study drug. Cardiovascular events frequently occur in association with the Cialis use. However, these events can not always be clearly attributed to the drug.

Frequent adverse events:

The most frequently reported TEAEs in tadalafil-treated subjects in this study were headache (15.7%), back pain (8.8%), dyspepsia (7.5%), and nasal congestion (4.4%). There were no reports of color vision abnormalities. (Table 15)

Table 15. Study LVEF; Summary of Treatment-Emergent Adverse Events (>2%) of All Randomized Subjects

Event	Placebo (N=48)		IC 20mg (N=159)		p-Value
	n	(%)	n	(%)	
Headache NOS	3	(6.3)	25	(15.7)	.146
Back pain	0		14	(8.8)	.043
Dyspepsia	0		12	(7.5)	.072
Nasal congestion	0		7	(4.4)	.357
Fatigue	0		5	(3.1)	.592
Bronchitis NOS	0		4	(2.5)	.575
Chest pain	0		4	(2.5)	.575
Cough	0		4	(2.5)	.575
Diarrhoea NOS	1	(2.1)	4	(2.5)	1.00
Flushing	0		4	(2.5)	.575
Hypertension NOS	0		4	(2.5)	.575
Pain in limb	0		4	(2.5)	.575

*Source Table LVEF.4.13

Reviewer's Comments: These frequently seen TEAEs in LVEF are consistent with the known adverse event profile of Cialis.

Changes in laboratory values:

There were no clinically significant differences between tadalafil and placebo in laboratory analyses as assessed by mean change from baseline to endpoint, baseline to

minimum, or baseline to maximum. A few changes in the haematological values and LFT's were noted without obvious pattern or clinical significance.

Reviewer's comment: There were no new laboratory safety data to preclude approval of Cialis.

Vital signs: There was no clinically significant change in heart rate or blood pressure in the placebo or drug groups.

Reviewer's assessment of efficacy and safety for Study LVEF: In the opinion of this reviewer, the safety and efficacy data presented in Trial LVEF support approval of Cialis 20mg for the treatment of male erectile dysfunction. They are consistent with previous Phase 3 trials.

3.8.1.2. Study LVCR:

This study was a U.S., multi-center (20 sites), randomized, double-blind, parallel, placebo-controlled study to evaluate the efficacy and safety of on-demand dosing of 20 mg tadalafil or placebo administered for 12 weeks to men with ED. After a 4-week treatment-free run-in period, approximately 210 subjects were stratified by IIEF Erectile Function Domain score as follows: mild ED = 17 through 30, moderate ED = 11 through 16, severe ED = 1 through 10. They were then randomly assigned within each severity group into treatment groups in a 1:3 (placebo: 20 mg tadalafil) fashion. This was followed by a treatment period that lasted approximately 12 weeks.

According to the sponsor, after a 4-week treatment-free run-in period, 195 subjects were stratified by IIEF Erectile Function Domain score as follows: mild ED = 17 through 30, moderate ED = 11 through 16, severe ED = 1 through 10. They were then randomly assigned within each severity group into treatment groups in a 1:3 (placebo: 20 mg tadalafil) fashion. This was followed by a treatment period that lasted approximately 12 weeks. 147 patients (75.4%) completed this study. Of the 18 placebo patients (36.8%) who discontinued the study, half 9 discontinued due to a perceived lack of efficacy. Of

the 30 IC351-treated patients (20.6%) who discontinued the study, 8 (5.5%) discontinued due to lack of efficacy and 8 (5.5%) discontinued due to an adverse event.

Demographics: The mean age of all patients enrolled was approximately 60 years. The majority of patients were Caucasian, accounting for 87.8% of patients assigned to the placebo group and 81.5% of patients assigned to the 20 mg IC351 treatment group. African-Americans accounted for 12.2% of patients assigned to the placebo group and 15.8% of patients assigned to the 20 mg IC351 treatment group. There were 2% Hispanics in the Cialis 20mg group. The mean weight of all patients at baseline was approximately 92 kg. Baseline IIEF EF severity was well balanced between the placebo and IC351-treatment groups. The percentage of patients with mild disease in both groups was approximately 33% while the percentage of patients with either moderate disease or severe disease in both groups was approximately 17% and 50%, respectively.

Reviewer's Comments: The treatment groups were well balanced. The demographics of this study are acceptable.

Efficacy analysis:

Table 16: Study LVCR: Summary of Primary Efficacy Variables, All Randomized Subjects.

	Placebo (N=49)	CIALIS 20mg (N=146)	p-value
EF Domain Score			
Endpoint	13.5	19.5	
Change from baseline	-0.2	6.8	<.001
Insertion of Penis (SEP2)			
Endpoint	39%	62%	
Change from baseline	2%	26%	<.001
Maintenance of Erection (SEP3)			
Endpoint	25%	50%	
Change from baseline	5%	33%	<.001

*Source: Table LVCR 4.4

Reviewer's assessment of efficacy in Study LVCR: Tadalafil 20mg demonstrated a clinically meaningful and statistically significant improvement in the ED endpoints tested in this population.

Safety analysis:

According to the sponsor, of placebo patients, 22.4% reported at least one adverse event during the study whereas of the IC351-treated patients, 41.8% reported at least one adverse event. There was a significant difference ($p = 0.017$) between the two groups with regard to the overall incidence of treatment emergent adverse events. Among the most frequently reported treatment-emergent adverse events in IC351-treated patients in this study were headache (8.9%), pain (6.2%), dyspepsia (4.8%), myalgia (3.4%), and rhinitis (2.7%).

Thirteen patients (8.9%) in the IC351 treatment group reported headache while no patient in the placebo group reported this adverse event. Nine patients (6.2%) in the IC351 treatment group and 1 patient (2.0%) in the placebo group reported pain (Table 17).

Table 17. Treatment-Emergent Adverse Events(>2%) all randomized subjects

Adverse Event	Placebo (N=49)		IC_20mg (N=146)		p-Value*
	n	(%)	n	(%)	
HEADACHE	0		13	(8.9)	.041
PAIN	1	(2.0)	9	(6.2)	.456
DYSPEPSIA	0		7	(4.8)	.195
INFECTION	0		6	(4.1)	.340
MYALGIA	0		5	(3.4)	.333
DIARRHEA	0		4	(2.7)	.574
RHINITIS	0		4	(2.7)	.574
COUGH INCREASED	0		3	(2.1)	

*Source:LVCR 4.13

Deaths and Serious Adverse Events:

No deaths occurred in this study. Four patients (2%) experienced serious adverse events in this study. Of the 4 patients who experienced a serious adverse event, 3 occurred in patients treated with IC351 (mild carotid occlusion, neoplasm, and esophagitis) and 1 occurred in a patient treated with placebo (chest pain).

Discontinuations due to adverse event:

Nine patients discontinued the study due to clinically significant adverse events. One patient (814-8510) discontinued the study due to a serious adverse event. Eight patients (1 on placebo and 7 on IC351) discontinued the study.

Reviewer's comment: This reviewer agrees with sponsor and investigators that none of the SAE's were attributed to the drug.

Changes in laboratory values:

There were no clinically significant differences between tadalafil and placebo in laboratory analyses mean change from baseline to endpoint in any vital sign.

Reviewer's comment: There were no new laboratory safety data to preclude the approval of this drug.

Vital signs: There was no clinically significant change in heart rate or blood pressure in the placebo or drug groups.

Reviewer's assessment of efficacy and safety for Study LVCR: In the opinion of this reviewer, the safety and efficacy data presented in Trial LVCR support the approval of Cialis 20mg for the treatment of erectile dysfunction.

3.8.1.3. Study LVCI:

This was a randomized, double-blind, placebo-controlled study of the efficacy and safety of tadalafil administered to patients with erectile dysfunction following bilateral nerve-sparing radical retropubic prostatectomy. (Dates of the study: 28 February 2002- 09 December 2002)

The primary objectives of this study was to evaluate the efficacy of 20 mg tadalafil, in comparison with placebo, in men with erectile dysfunction (ED) following bilateral nerve-sparing radical retropubic prostatectomy (BNP) who show some evidence of post-operative potency.

Primary efficacy was measured by the Erectile Function (EF) Domain of the International Index of Erectile Function (IIEF, Questions 1-5 and 15), Question 2 of the SEP diary, and Question 3 of the SEP diary.

According to the sponsor, the study consisted of two periods. The first period was a run-in period that lasted approximately 4 weeks. The 28-day run-in period began when the subject had signed the ICD. After the run-in period, the subject returned for Visit 2 and was assessed for enrollment eligibility. If enrolled, the subject began the treatment period, which lasted approximately 12 weeks. The 12-week treatment period consisted of three distinct segments, each approximately 4 weeks in duration. Visit 3 occurred after the first 4 weeks of treatment, Visit 4 occurred after the second 4 weeks of treatment, and Visit 5, the final visit, occurred after the third 4 weeks of treatment. 161 patients in the 20-mg tadalafil group and 76 in the placebo group completed the study.

Study LVCI Patient Selection Criteria

Subjects participating in this study must have developed ED (defined as a consistent change in the quality of erection that adversely effects the subject's satisfaction with sexual intercourse) as a result of having undergone BNP.

Inclusion Criteria

Subjects were included in the study only if they met all of the following criteria:

- [1] Men, at least 18 years of age at Visit 1 and 65 years of age or younger at the time of BNP willing to participate in the study.
- [2] Provide signed informed consent.
- [3] Developed ED (defined as a consistent change in the quality of erection that adversely affects the subject's satisfaction with sexual intercourse) subsequent to having undergone BNP.
- [4] Make at least four sexual intercourse attempts during the 4-week run in period without medication.
- [5] Agree not to use any other ED treatment for at least 4 weeks before receiving the initial dose of study drug (that is, during the run-in the final study visit is completed).

[6] Have had BNP, documented at time of surgery, within 12 to 48 months before screening and were documented to be potent before having BNP.

[7] The stage of prostate cancer must be \leq PT3 as indicated by the pathology report post-operatively

Exclusion Criteria

Subjects were excluded from the study for any of the following reasons:

[1] Impotence caused by other primary sexual disorders including premature ejaculation or impotence caused by untreated endocrine disease (e.g. hypopituitarism, hypothyroidism, or hypogonadism).

[2] History of pelvic surgery other than BNP.

[3] History of penile implant.

[4] The presence of clinically significant penile deformity in the opinion of the investigator.

[5] Evidence of clinically significant renal insufficiency within the last 6 months before Visit 1.

[6] Active symptomatic hepatobiliary disease, including subjects with evidence of jaundice at Visit 1.

[7] Hemoglobin A1c $>13\%$ at Visit 1.

[8] Subjects with chronic stable angina treated with long-acting nitrates, or subjects with chronic stable angina who have required short-acting nitrates in the last 90 days, or angina occurring during sexual intercourse in the last 6 months.

[9] Subjects having met the criteria for unstable angina within 6 months before Visit 1, history of myocardial infarction or coronary artery bypass graft surgery within 90 days before Visit 1, or percutaneous coronary intervention (for example, angioplasty or stent placement) within 90 days before Visit 1.

[10] Any supraventricular arrhythmia with an uncontrolled ventricular response (mean heart rate >100 bpm) at rest despite medical or device therapy, or any history of spontaneous or induced sustained ventricular tachycardia (heart rate >100 bpm for ≥ 30 sec) despite medical or device therapy, or the presence of an automatic internal cardioverter defibrillator.

- [11] A history of sudden cardiac arrest despite medical or device therapy.
- [12] A new, significant conduction defect within 90 days before Visit 1.
- [13] Systolic blood pressure >170 or <90 mm Hg or diastolic blood pressure >100 or <50 mm Hg at screening (if stress is suspected, retest under basal conditions), or subjects with a history of malignant hypertension.
- [14] History of significant central nervous system injuries (including stroke and spinal cord injury) within the 6 months before Visit 1.
- [15] History of HIV infection.
- [16] Any condition that would interfere with the subject's ability to provide informed consent or comply with study instructions, would place subject at increased risk, or might confound the interpretation of the study results.
- [17] Current treatment with nitrates, cancer chemotherapy, or anti-androgens.
- [18] History of drug, alcohol, or substance abuse within the 6 months before Visit 1.
- [19] Have a prostate specific antigen (PSA) level that is detectable at Visit 1.
- [20] Have undergone, or plan to undergo, radiation or hormonal therapy for prostate cancer.
- [21] Persons who have previously completed or discontinued from this study or any other study investigating tadalafil are not eligible to participate in this study.
- [23] Treatment within the 30 days before Visit 1 with a drug or device that has not received regulatory approval.
- [24] Have any condition, limitation, or disease that could, in the judgment of the investigator, preclude evaluation of response to tadalafil.

Reviewer's Comment: The trial design, conduct and patient selection are acceptable.

Study LVCI Statistical Methods:

According to the sponsor, a sample size of 300 subjects was calculated to provide over 80% power to detect a significant treatment effect in each of the three co-primary endpoints for each of the two populations at a two-sided alpha level of 0.025. An alpha of

0.025 represents a conservative adjustment for the multiple comparison based on the two populations being tested. There was no alpha adjustment for the three co-primaries since all three coprimaries must reach statistical significance in order for the null hypothesis to be rejected. The sample size was driven by the SEP Question 2 analysis in the entire subject population. The treatment effect used in the sample size calculation for this study is based on 60% of that seen in the studies of tadalafil previously mentioned.

Protocol Violations:

There were a total of 25 protocol violations that were considered significant as previously defined. These violations included ten related to study drug administration, five to informed consent, seven to entry criteria, one to review of screening laboratory results, one error in data entry of IIEF data into the randomization system, and one laboratory data issue described in the paragraph below. In this reviewer’s opinion these protocol violations did not affect the validity of the study conclusions.

Efficacy Results from Study LVCI:

Table 18: Summary of Primary Efficacy Variables, All Randomized Subjects (LVCI):

	All (N=303)	Placebo (N=102)		Cialis 20mg (N=201)		
	BASELINE	END	CHG	END	CHG	P
IIEF Domains						
Erectile Function	12.4	13.3	1.1	17.7	5.3	<.001
Patient SEP Questions						
SEP2 - Insert Penis into Vagina	31.7	32.4	1.9	53.9	21.6	<.001
SEP3- Successful Intercourse	16.9	19.4	3.7	40.5	23.0	<.001

*Source, Table LVCI.11.3.

Table 19: Summary of Primary Efficacy Variables; All Randomized Subjects with Some Evidence of Post-Operative Potency (LVCI)

	All	Placebo		Cialis 20mg		
	(N=201)	(N=68)		(N=133)		
	BASE	END	CHG	END	CHG	P
IIEF Domains						
Erectile Function	15.1	15.2	0.4	21.0	5.9	<.001
Patient SEP Questions						
SEP 2 - Insert Penis into Vagina	45.6	41.9	-1.1	69.1	22.2	<.001
SEP 3 - Successful Intercourse	24.8	26.1	2.8	52.4	26.9	<.001

*Source, Table LVCI.11.9.

Reviewer's assessment of efficacy: Tadalafil 20mg demonstrated a clinically meaningful and statistically significant improvement in the ED endpoints tested in this population following BNP.

Safety Results from Study LVCI:

Treatment-Emergent Adverse Events:

Of the 102 placebo subjects, 27 (26.5%) reported at least one TEAE, whereas 104 (51.7%) of the 201 subjects on 20 mg tadalafil reported at least one TEAE. The TEAEs reported by >5% of all subjects or by >5% of subjects receiving tadalafil were headache (20.9% in the 20-mg tadalafil group and 5.9% in the placebo group), dyspepsia (13.4% in the 20-mg tadalafil group and 1.0% in the placebo group), and myalgia (6.5% in the 20-mg tadalafil group and 0% in the placebo group)

Table 20. Treatment-Emergent Adverse Events (>2%) in Subjects Receiving Tadalafil All Randomized Subjects(LVCI)

EVENT	Placebo		Cialis 20mg		p-Value*
	(N=102)		(N=201)		
	n	(%)	n	(%)	
Headache NOS	6	(5.9)	42	(20.9)	<.001
Dyspepsia	1	(1.0)	27	(13.4)	<.001
Myalgia	0		13	(6.5)	.006
Back pain	6	(5.9)	9	(4.5)	.586
Nasal congestion	1	(1.0)	9	(4.5)	.173
Fatigue	1	(1.0)	7	(3.5)	.275
Flushing	0		7	(3.5)	.100
Sinus congestion	0		5	(2.5)	.172

*Source : LVCI.12.3.

Deaths:

No deaths occurred in the present study.

Serious and Clinically Significant Adverse Events:

One subject in the placebo group experienced SAEs after randomization. Subject 810-9353 on placebo experienced two SAE's (brain neoplasm and pulmonary embolism) after randomization.

Reviewer's Comment: There were no new adverse events in this trial to preclude the approval of Cialis.

Clinical Laboratory Evaluation

The screening prostate specific antigen (PSA) laboratory results for 40 subjects may have been invalid due to data manipulation by a technician at the central laboratory

Overall Assessment of Efficacy and Safety in Study LVCI:

In the opinion of this reviewer, the safety and efficacy data presented in trial LVCI support the approval of Cialis 20mg for the treatment of erectile dysfunction in ED patients following BNP.

3.8.1.4. "Effectiveness"

Regulatory History

On 08 August 2002, the sponsor submitted the protocol for Study LVFD. On 07 October 2002, a teleconference was held and the sponsor was advised that the language for labeling needs to be explicit regarding what was observed during the clinical trials; Sponsor may propose language for labeling on resubmission and that wording for dosing instructions will be a review issue.

Sponsor's Response:

The sponsor submitted the report for Study LVFD, assessing the efficacy of both 10 mg and 20 mg tadalafil at 24 and 36 hours following dosing. The sponsor also submitted an analysis of the data from Phase 3 clinical studies regarding the — of effectiveness as well as an analysis of data from 2 studies from the original NDA (Studies LVCK and LVDG).

- Study LVCK examined — of effectiveness for 10 mg and 20 mg tadalafil within the first 30 minutes after dosing (Data beyond 30 minutes was not collected).
- Study LVDG examined effectiveness of tadalafil in sexual attempts occurring at 24 or 36 hours post-dose.

The data from the previously submitted studies have been reviewed before. A review of LVFD is presented along with the overall conclusion from the studies.

Study LVFD:

This study was a multicenter, randomized, double-blind, placebo-controlled, parallel design study to evaluate the efficacy and safety of 10 mg tadalafil, 20 mg tadalafil, or placebo when sexual activity, in men with ED, occurs at prespecified time points after dosing.

According to the sponsor, the baseline for analysis was a 4-week run-in phase, during which the subjects did not use any form of treatment for ED. During the “equilibration phase”, which lasted up to 4 weeks, the subjects were given a supply of study drug to take as desired up to once daily at any time prior to expected sexual activity. During the “assessment phase”, which lasted up to 6 weeks, subjects were asked to take four doses of study drug, each dose separated by at least 7 days, and each followed by a sexual attempt at the assigned time after dosing.

This study randomized 483 subjects in the United States to six groups in a 1:1:1:1:1:1 ratio, one group for each combination of treatment (placebo, 10 mg tadalafil, or 20 mg tadalafil) and assigned time (24 or 36 hours).

An evaluable attempt was defined as a sexual attempt that met all the following criteria:

1. It was the first attempt after a treatment dose.
2. It occurred within the subject's assigned window post dose (between 22 and 26 hours post-dose for the 24-hour assigned time, and between 33 and 39 hours post dose for the 36-hour assigned time).
3. SEP diary data were recorded for it.

Only attempts during the "assessment phase" of the study were assessed as evaluable or non-evaluable. For each SEP question, the baseline score was the subject's percentage of "yes" responses to that question relative to the number of sexual attempts during the Run-In phase (Visit 1 to Visit 2); and the Assessment phase score was the subject's percentage of "yes" responses regarding evaluable attempts relative to his total number of evaluable attempts during the Assessment phase (between Visit 3 and Visit 4).

Reviewer's Comments: In the opinion of the reviewer, the study design permits one to distinguish an effect of treatment with Cialis at given time points (24 and 36 hours).

Efficacy Results for Study LVFD:

1. The mean percentages of sexual attempts at 24 hours that were successful on 20 and 10 mg tadalafil were 67.3% and 55.8%, respectively, compared with 41.8% on placebo.
2. The mean percentages of sexual attempts at 36 hours that were successful on 20 and 10 mg tadalafil were 61.9% and 56.2%, respectively, compared with 32.8% on placebo.
3. Statistical significance in favor of Cialis was $p=0.038$ for 10 mg versus placebo at the 24-hour assigned time, and $p < 0.001$ for the other three pair wise comparisons.

Reviewer's Comments:

- The results of the study LVFD suggest that there are clearly distinguishable differences between placebo and Cialis. These results are similar to those seen in the study LVDG. Also, the separation between the drug and placebo is more pronounced at 30 minutes.
- Study LVCK showed that, at 30 minutes: 34.0% of 300 attempts in the 20 mg tadalafil group were successful, compared with 17.6% of 284 attempts in the placebo group (p=0.002). The one hour data in this study was not available.
- The deduction one can make from the study LVCK is that 65% of the patients on tadalafil had at least one successful intercourse in four attempts in the first 30 minutes following administration of Cialis. (see Biometrics reviews, included Dr. Welch's review)

3.9. Starting Dose for TadalafilThe approvable letter states:

“We have completed our review and find your application, as amended, for marketing of Cialis 5 mg, 10 mg, and 20 mg tablets is approvable. Your efficacy data demonstrate that 10 mg would be an appropriate starting dose for most men with erectile dysfunction. The FDA believes that a range of dosage strengths are needed to promote effective treatment of the spectrum of erectile dysfunction and to promote safety through use of the lowest effective dose.”

Regulatory History

On 20 February 2002, DRUDP asked the sponsor to provide additional justification for pursuing 20 mg as the only dose.

On 04 March 2003, DRUDP communicated to the sponsor that starting dose would be a review issue. The question of whether 20 mg provides greater efficacy and similar safety as 10 mg also will be a review issue.

Sponsor's Response

The sponsor presented a case for 20mg as a starting dose. Essentially, the sponsor contends that substantial new information regarding overall safety that supports 20mg as just as safe and tolerable as 10mg (exposure = 3102 patients: 1,027 subjects exposed to

20 mg tadalafil for 6 months or more and 586 subjects exposed to 20 mg tadalafil for 1 year or more in the open-label studies). Therefore, in sponsor's opinion, if safety and tolerability are without difference and if it is possible that 20mg is more effective than 10mg, then a given patient should have his "best chance" at efficacy right from the first dose. In sum, the sponsor believes that the higher starting dose can be justified if there is an efficacy advantage resulting in an improvement in the benefit: risk ratio. The sponsor contends that the safety profile for 20 mg is no worse than the 10mg dose. The entire new safety database was reviewed.

Reviewer's Comments:

1. From the efficacy review of all comparable trials where 10mg and 20mg doses were used, it is clear that there is virtually no clinically meaningful difference between the effect size of 10 and 20mg. Therefore 10mg appears to be an optimal starting dose in the general population. This can be titrated up or down as needed. Additionally, Cialis 5 mg is recommended in moderate to severe renal impairment and 10mg (Q 72 hours) is recommended in patients with concomitant use of CYP3A4 inhibitors.
2. Due to the long half-life of Cialis and its associated interactions with nitrates, alcohol and alpha-adrenergic antagonists, a 10 mg dose (rather than 20mg) as a starting dose is desirable.
3. The safety data from placebo-controlled trials shows a clear dose related increase in the adverse events specifically headache, backache and dyspepsia.

Table 21. Treatment-Emergent Adverse Events Reported by >2% of Patients Treated with Tadalafil (10 or 20 mg) the Eight Primary, Placebo-Controlled Phase 3 Studies (including Study LVBK in Diabetics)

Adverse Event	Placebo (N=476)	Tadalafil 5mg (N= 151)	Tadalafil 10mg (N=394)	Tadalafil 20mg (N=635)
Headache	5%	11%	11%	15%
Dyspepsia	2%	4%	8%	10%
Back pain	3%	3%	5%	6%

Overall assessment of the response regarding starting dose:

This reviewer believes that:

1. Cialis 10mg is an optimum starting dose for the general ED population. This can be titrated up or down as needed.
2. In patients who require concomitant use of ketoconazole and HIV protease inhibitors, Cialis should be dosed at 10mg Q 72 hours.
3. The starting dose of Cialis in patients with moderate to severe renal impairment should be 5mg daily.(Please see the section on myalgia/ back pain as well.)

3.10. Safety Updates:

The sponsor was asked to submit all the updated information regarding the safety of Cialis along with new marketing information from foreign markets approvals. According to the sponsor, Tadalafil was first approved on 15 October 2002 in Australia and as of April 2003, it has been approved in 20 countries. Approximately _____ tablets of tadalafil have been sold representing an estimated total exposure of _____ patients. In the Complete Response, the sponsor submitted two safety updates. Both the safety updates were reviewed.

3.10.1. Study Drug Exposure

According to the sponsor, as of 01 March 2003, 8925 patients have participated in various tadalafil studies. Of the 8925 patients, 7029 received tadalafil, 1894 received placebo, and 877 received an active control drug. 2088 patients were actively participating in clinical trials as of March 2003 (April Update). The total patient exposure to all doses of market image tadalafil in the clinical studies is approximately 2620 patient-years (10 or 20 mg tadalafil = 2532.53 patient-years). A total of 1707 patients were exposed to tadalafil in the long-term, open-label studies, of whom 574 were exposed to tadalafil for the first time (see Table 22).

Table 24: Long term exposure to tadalafil*

Study	Number of Patients Receiving Tadalafil
LVBL*	1173
LVBD	203
LVBE	194
LVDR	331
TOTAL	1707

*Additional 561 enrolled after interim conclusion.

3.10.2. Primary placebo-controlled pooled studies safety database:

Demographics:

According to the sponsor, a total of 2071 (of 2088 participating) patients were randomized to treatment with either placebo (569 patients) or tadalafil (1502 patients) in the primary placebo controlled studies. Of the total patient population in these studies, 76.9% were Caucasians, 15.8% were East or Southeast Asian, 3.2% were of African descent, 3.1% were Hispanic, and 0.6% were Western Asians. The mean age of patients in these studies was 57.5 years, and the ages ranged from 22 to 88 years. 23.7% of patients were smokers, 61.8% used alcohol with a mean intake of 4.9 units per week. 27.7% had a history of diabetes mellitus. 30.6% had a history of hypertension. 5.5% had a history of coronary artery disease, 34.6% had a history of vascular disorder including hypertension, 17.8% had a history of hyperlipidemia, and 5.1% had a history of depression.

Reviewer's Comments: The demographic profile submitted in this submission is similar to the one submitted in the original NDA and well reflects the broad ED population.

Deaths, Discontinuations and Adverse Reactions Primary PC Studies:

1. No deaths were reported.
2. 87.6% of tadalafil-treated patients [10- and 20-mg doses combined] and 86.5% of placebo-treated patients completed their study.
3. The rate of discontinuations because of adverse events was 3.1% for tadalafil-treated patients [10- and 20-mg doses combined] and 1.4% for placebo-treated patients.

4. Headache (14.6%), dyspepsia (9.1%), back pain (5.4%), flushing (3.3%), myalgia (3.2%), pain in limb (3.1%), and nasal congestion (2.7%) were the most frequently reported adverse events in >2% of tadalafil-treated patients.
5. No clinically significant differences were found in mean changes-from-baseline to endpoint in vital sign measurements among treatment groups during these studies.
6. The adverse event profile was similar in patients >65 and <65 years of age, in patients on anti-hypertensive medications, and in patients with hypertension, diabetes, coronary artery disease, vascular disorders or hyperlipidemia.
7. The incidence of serious adverse events (SAE's) was 1.1% (17/1502) among tadalafil-treated patients (10- and 20-mg doses combined) and 1.6% (9/569) among placebo-treated patients in the primary placebo-controlled safety database. Patient 117-9703 (Placebo group) in Study LVBK and patient 024-2152 (Placebo group) in Study LVDJ experienced myocardial infarction.

Reviewer's Comments: No new safety concerns were raised in the data submitted. The cardiac events have been reviewed in the section on cardiovascular events, however the events can not be definitively attributed to the use of Cialis.

3.10.3. Primary Long -Term Pooled Safety Studies - LVBL and LVDR

According to the sponsor, of 1504 patients enrolled in these long-term, open-label studies, 1173 were enrolled in Study LVBL and 331 were enrolled in Study LVDR. The baseline patient demographics and other characteristics were comparable between the two studies.

Demographics (LVBL and LVDR):

LVBL:

Of the 1173 male patients enrolled in Study LVBL, 94.6% were Caucasian, 1.7% were of African descent, 2.0% were Hispanic, 1.0% were Western Asian, 0.3% were East or Southeast Asian, and 0.3% were categorized as "Other." The mean age of the 1173 patients enrolled in Study LVBL was 57.0 years; 930 patients (79.3%) were <65 years of age and 243 patients (20.7%) were >65 years of age. The mean weight of patients enrolled in Study LVBL was 85.2 kg. At baseline, 25.5% of these patients were smokers and 69.0% consumed a mean alcohol intake of 4.8 units per week.

LVDR:

Of the 331 male patients enrolled in Study LVDR, 97.3% were Caucasian, 0.6% were of African descent, 0.6% were Hispanic, 0.3% were Western Asian, and 1.2% were East or Southeast Asian. The mean age of the 331 patients enrolled in Study LVDR was 59.5 years; 231 patients (69.8%) were <65 years of age and 100 patients (30.2%) were >65 years of age. The mean weight of patients enrolled in Study LVDR was 86.9 kg. At baseline, 15.4% of these patients were smokers and 76.7% consumed a mean alcohol intake of 7.1 units per week.

Reviewer's Comments: The demographic profiles submitted in studies LVBL and LVDR are similar to the one submitted in the original NDA and represent the broad ED population.

Patient Exposure to Study Drug:

Table 25 shows the patients exposure to Cialis in LVBL and LVDR.

Table 25: Exposure to Study Drug in Primary Open-Label, Long-Term Pooled Studies Studies LVBL (Interim 2) and LVDR

Days on Therapy	LVBL*	LVDR	Total
	(N=1173)	(N=331)	(N=1504)
No. Patients	1172	331	1503
Mean	397.65	173.85	348.36
Median	453.50	182.00	418.00
Standard Dev.	150.87	32.02	163.03
Minimum			
Maximum			

Source: Table 6.3 Safety Update, *Interim 2

Reviewer's Comments: The patient exposure to Cialis is adequate and within ICH guidelines.

Patient Disposition:

1504 patients were enrolled in the studies LVBL and LVDR. Of these, 1173 were enrolled in Study LVBL and 331 were enrolled in Study LVDR. Of the 331 patients enrolled in Study LVDR, 300 (90.6%) completed the study protocol. Of the 1504 patients in this pooled open-label, long-term safety database, 73 patients (6.2 %) discontinued

because of adverse events. Seven deaths were also reported in these studies, none appeared to be related to drug. (See section on Deaths below).

Other discontinuations in this pooled database were attributed to the following:

1. 10 patients (0.5%; 8 patients were in Study LVBL and 2 patients were in Study LVDR) because of the Sponsor's decision to discontinue the patient for reasons other than the termination of Study LVBL at Visit 8 (see below)
2. 179 patients (11.9%; 14.3% in Study LVBL and 3.3% in Study LVDR) because of patient- and physician-perceived lack of efficacy.
3. 80 patients (5.3%; 6.3% in Study LVBL and 1.8% in Study LVDR) because of personal conflict or other patient decision.
4. The 231 patients in Study LVBL who discontinued because of the Sponsor's decision were discontinued because the Sponsor decided to end the study early.

Reviewer' Comments: The discontinuations and drug unrelated deaths do not raise concerns nor preclude the approval of Cialis.

Deaths

According to the sponsor, five patient deaths occurred during these studies and two patient deaths occurred after the patients discontinued from their study because of adverse events. Of the four deaths that occurred in Study LVBL, none were attributed to tadalafil administration. All of these deaths have been reported previously. One death was reported in the most recent PSUR with possible attribution to Cialis. The identification numbers for the patients who died are the following:

1. Clinical trial case US_030393333 (PSUR APRIL 2003) concerned a 55 year old male whose medical history included non-specific ECG changes, dyspnea, hypertension, diabetes, obesity and a history of heavy smoking. Concomitant medication included metformin, glibenclamide, lisinopril, ketofan, diclofenac, aspirin, and pravastatin. Approximately two months after beginning tadalafil (20mg), the patient experienced cardiac arrest and died. An autopsy was not performed. The investigator reported that the death was due to a "possible cardiac arrest or ventricular fibrillation following a

myocardial infarction a few days before” and the event of cardiac arrest was possible related to study drug and protocol procedures.

2. 003-4065(PSUR 24 September 2001): probable cardiac arrest secondary to coronary artery disease.
3. 007-3072: cardiac arrest secondary to hypertensive and coronary artery disease (Study LVBL : Interim 1)
4. 009-0273: suicide by hanging (reported in the clinical study report for Study LVBL : Interim 1)
5. 105-2107: cardiac arrest after aspiration pneumonia (reported as a late death in the original NDA submission of 28 June 2001).
6. Two patients who discontinued from Study LVBL because of adverse events died subsequent to their discontinuations for these events (see Patient disposition section).

Reviewer’s Comments: None of these deaths can be definitely attributed to Cialis.

Serious Adverse Events

Table 26 shows the SAE’s in the long-term studies. The reader is also referred to section on cardiovascular events.

**APPEARS THIS WAY
ON ORIGINAL**

Table 26: All patients enrolled in the primary open-label, long-term pooled safety studies, by study and for both studies combined, by decreasing frequency (*>0.1%).

Event	LVBL* (Interim -2) (**)		LVDR		Total	
	(N=1173)		(N=331)		(N=1504)	
	n	(%)	n	(%)	n	(%)
Myocardial infarction	6	(0.5)	1	(0.3)	7	(0.5)
Inguinal hernia NOS	3	(0.3)	1	(0.3)	4	(0.3)
Atrial fibrillation	3	(0.3)	0		3	(0.2)
Cardiac arrest	3	(0.3)	0		3	(0.2)
Cerebrovascular accident	3	(0.3)	0		3	(0.2)
Pneumonia NOS	2	(0.2)	1	(0.3)	3	(0.2)
Acute myocardial infarction	2	(0.2)	0		2	(0.1)
Angina pectoris	2	(0.2)	0		2	(0.1)
Chest pain	2	(0.2)	0		2	(0.1)
Cholecystitis NOS	2	(0.2)	0		2	(0.1)
Colon cancer NOS	2	(0.2)	0		2	(0.1)
Hip fracture	2	(0.2)	0		2	(0.1)
Intervertebral disc herniation	2	(0.2)	0		2	(0.1)
Pancreatitis NOS	2	(0.2)	0		2	(0.1)

*(Interim-2 cut off data) 1 case each of: cardiac failure, angina, atrial flutter, cerebral infarction, hematemesis, MI, pulmonary embolism occurred in <0.1%.

** (completed data) The 5 other serious, unlisted reactions were: cardiac arrest, bradycardia, angina pectoris, coronary artery disease, and myocardial infarction in the most recent update.

According to the sponsor, of the 1504 patients in this pooled safety database the completed analysis on LVBL showed that in Study LVBL, 101 subjects (8.6%) and 3.9% in Study LVDR experienced one or more SAE's.

Of these subjects, 7 experienced an SAE thought by the sponsor to be possibly related to tadalafil treatment: myocardial infarction (Subjects 405-1064 and 007-0236), atrial fibrillation (Subject 412-1147), atrial fibrillation and cerebral infarction (Subject 408-1084), angina pectoris (Subject 405-1056), haematemesis (Subject 005- 4118), and loss of consciousness (Subject 005-0201)

Three subjects experienced cardiac arrest: 003-4065, 007-3072, and 105-2107 (Subject 105-2107 also experienced acute myocardial infarction).

Fifteen subjects experienced myocardial infarction/ischemia/possible ischemic symptoms: 002-0126, 002-4017, 003-4062, 007-0232, 007-0236, 009-0275, 009-0279, 018-4339, 102-2036, 105-2102, 105-2107 (Subject 105-2107 also experienced cardiac arrest), 220-3256, 405-1056, 405-1064, and 418-1296.

Two subjects experienced congestive heart failure events: 107-2152 and 211-3134. Four subjects experienced supraventricular arrhythmia events: 408-1084, 211-3148, 405-1057, and 412-1147.

Two subjects experienced syncope/hypotension/possible hypotensive events: 003-4059 and 005-0201.

One subject experienced pulmonary hypertension: 211-3134 (this patient also experienced cardiac failure).

Seven subjects experienced cerebrovascular events: 004-4087, 009-0280, 208-3121, 208-4391, 408-1084, 411-1113, and 411-1129.

Reviewer's Comments: (The reader is also referred to section on cardiovascular events)

1. Many, if not most, ED patients have associated co-morbid cardiovascular conditions. It will be important for medical practitioners to try to identify the patients at risk for potential cardiovascular ischemia who may eventually need nitrates and try to restrict the use of tadalafil from such patients.
2. The coadministration of Cialis with nitrates is contraindicated. The sponsor has mitigated some safety concerns by conducting a trial (LVDN) to show the duration of interaction between Cialis and nitrates. There is an interaction that lasts up to 48 hours. Patients who need nitrate administration following intake of Cialis require close and intense medical supervision.
3. The serious adverse event profile submitted in the updates is similar to the one submitted originally in NDA 21-368.
4. The cardiovascular cases described above cannot be attributed to Cialis.

Treatment Emergent Adverse Events (TEAE):

Table 27 shows TEAE's in > 2% of the subjects in the open label studies.

Table 27: Summary of Treatment-Emergent Adverse Events Occurring in >2% of All Enrolled Patients By Study and by Decreasing Frequency Primary Open-Label Long-Term Pooled

	LVBL* (Interim 2) (N = 1173)	LVDR (N = 331)	Total (N = 1504)
Preferred Term	n (%)	n (%)	n (%)
Headache NOS*	179 (15.3)	38 (11.5)	217 (14.4)
Dyspepsia*	131 (11.2)	31 (9.4)	162 (10.8)
Nasopharyngitis*	100 (8.5)	12 (3.6)	112 (7.4)
Back pain*	78 (6.6)	9 (2.7)	87 (5.8)
Flushing	39 (3.3)	14 (4.2)	53 (3.5)
Nasal congestion	39 (3.3)	10 (3.0)	49 (3.3)
Influenza	40 (3.4)	6 (1.8)	46 (3.1)
Arthralgia	36 (3.1)	7 (2.1)	43 (2.9)
Hypertension NOS	38 (3.2)	3 (0.9)	41 (2.7)
Myalgia	31 (2.6)	4 (1.2)	35 (2.3)
Influenza-like illness	34 (2.9)	--	34 (2.3)
Diarrhoea NOS	25 (2.1)	8 (2.4)	33 (2.2)
Dizziness	25 (2.1)	8 (2.4)	33 (2.2)
Cough	30 (2.6)	2 (0.6)	32 (2.1)

*Completed report incidences were: headache (15.8%), dyspepsia (11.8%), nasopharyngitis (11.4%), and back pain (8.2%).

Reviewer's Comment: The frequent adverse events reported in the safety updates are consistent with the already known safety profile of Cialis. These include: headache, dyspepsia, back pain, myalgia, flushing, and stuffy nose.

Vital Signs: No clinically significant differences were found in mean changes from baseline to endpoint in vital sign measurements during these studies.

Laboratory Evaluations: No clinically significant differences were found in mean changes from baseline to endpoint in clinical laboratory values during these studies.

Reviewer's Overall Assessment of Safety Update:

The recent safety updates and foreign marketing data revealed no new safety issues. The safety profile of this drug remains consistent. The following points are noteworthy:

1. The most common TEAE's reported by patients were headache, dyspepsia, nasopharyngitis, back pain, upper abdominal pain, myalgia, flushing, and nasal congestion.

2. The majority of the SAE's that were considered possibly related to tadalafil were cardiovascular. These have been reviewed in the cardiovascular event section of the review. These events cannot be definitively attributed to Cialis.
3. The rate of discontinuations because of adverse events was 4.7% in the pooled long-term studies. In the opinion of this reviewer, this very low long-term discontinuation rate reflects good tolerability.
4. No deaths were attributed to tadalafil treatment.
5. The sponsor also submitted secondary safety database on the 16 other studies. One is a completed study (LVDU), ten are ongoing studies (LVBL, LVEM, LVCI, LVDX, LVDZ, LVFD, LVEH, LVEI, LVEK, and LEVEL), three are ongoing studies for ED for which the pre-extension phase has been completed (LVCV, LVEB, and LVCG), and two are studies for other indications (I001 and LVDC). Safety review of the data submitted did not raise any additional safety concerns.

4.0. Overall Conclusions, Recommendations and Regulatory Action:

The sponsor has satisfactorily shown that Cialis is efficacious in the treatment of male erectile dysfunction in the general population, the diabetic patients and the patients who develop ED as a result of bilateral nerve sparing radical prostatectomy. The sponsor has adequately explored the safety issues identified in the approvable letter of April 29th, 2002. The sponsor has accepted the starting dose of this drug will be 10 mg in general population, 5 mg in the population with moderate to severe renal impairment and 10 mg every 72 hours in patients taking ketoconazole and ritonavir. Co-administration of Cialis with nitrates and alpha-blockers except tamsulosin (0.4mg) should be contraindicated. Excessive alcohol use is cautioned. Labeling is acceptable. The plan to monitor and manage selected risks is acceptable. ●

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mark S. Hirsch
11/21/03 05:09:42 AM
MEDICAL OFFICER
M.Hirsch signing for A.Batra (on leave)

Daniel A. Shames
11/21/03 08:44:54 AM
MEDICAL OFFICER

MEDICAL TEAM LEADER'S MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service**

**Food and Drug Administration
ODE 3**

Division of Reproductive and Urologic Drug Products (DRUDP)

Date: November 20, 2003

From: Mark S. Hirsch, M.D., Medical Team Leader, DRUDP

To: Daniel A. Shames, M.D., Division Director, DRUDP

Subject: NDA 21-368; Lilly ICOS LLC
Cialis® (tadalafil) tablets – for the treatment of erectile dysfunction (ED)
Complete Response to Approvable Action

1. Executive summary:

The purpose of this memo is to provide the Division Director with my recommendation for action on this NDA. I recommend **approval** of NDA 21-368; Cialis® (tadalafil) tablets – for the treatment of erectile dysfunction. The sponsor has submitted a Complete Response to Approvable Action that, in my opinion, fully addresses all previous outstanding issues. Adequate information has now been submitted to the Agency to assure safe and effective use of the product. Labeling negotiations have been successful in addressing all major safety and efficacy issues. At this point in the review, the labeling requires only minor revisions. A Phase 4 commitment to conduct an additional multiple dose vision study has been obtained. In addition, comments by Office of Drug Safety (ODS) have been managed by sponsor satisfactorily. I am now fully convinced that Cialis is effective in the treatment of ED, that it is safe for the intended use as labeled, and that the management of risk is maximized. In my opinion, there are no outstanding issues.

Reviewer's comment: Of note, at the time of completion of this memo, the Chemistry review was in draft form, but the Chemistry team informed me that there were no outstanding Chemistry deficiencies.

2. Brief summary of original deficiencies and the complete response:

2.1. Efficacy:

In the original NDA, the sponsor submitted the results of six Phase 3 trials conducted outside the U.S. These included a separate study in diabetics. All six trials confirmed the efficacy of Cialis® in the treatment of ED. However, there were two outstanding efficacy issues; first, the applicability of these efficacy results to the *U.S. population* was not fully known and second, the sponsor sought approval for a 20mg single *dosage strength* only.

2.1.1. *Applicability to the U.S. population*

In this Complete Response, the sponsor provided final study reports for two new Phase 3 U.S. pivotal trials (LVCR and LVEF). Each of these individually confirmed the efficacy of Cialis® in a broad and representative U.S. population. The efficacy and safety results of LVCR and LVEF

were consistent with those from trials conducted outside the U.S. The enrolled populations in the U.S. trials and the non-U.S. trials were reasonably similar in their background medical conditions and demographics. In the U.S. trials, there is adequate representation of non-White American groups (e.g. African-Americans and Hispanics), and these groups appeared to have benefits and risks consistent with the white American population. Thus, the issue of U.S. applicability is fully resolved.

2.1.2. *Dose selection*

In this Complete Response the sponsor applied for approval of two dosage strengths: 10mg and 20mg. In subsequent discussions with DRUDP, the sponsor agreed to market three dosage strengths (5mg, 10mg and 20mg) and to recommend use of these 3 doses in a titration paradigm. Specifically, labeling now recommends that most patients should start treatment at 10mg and then up- or down-titrate (or stay on 10mg) as necessary depending on their own personal efficacy and tolerability. The availability of the 5mg dose is also considered to be the appropriate starting dose for those patients with moderate or severe renal insufficiency, and the only dose for patients on dialysis. Based upon the sponsor's willingness to market a 5mg dose and to recommend the dose-titration paradigm, the issue of dose is fully resolved.

2.2. **Safety**

The review of the original NDA revealed several deficiencies in the submitted safety information. These focused on several major issues:

- a. drug-drug interactions (nitrates, alpha-blockers, alcohol, aspirin and warfarin),
- b. cardiovascular safety (detailed review of cardiovascular adverse events, submission of ongoing cardiac clinical studies, and assessment of drug effect on the QT interval),
- c. further investigation of back pain and myalgias reported as clinical adverse events.
- d. safety in special populations (diabetics and renal insufficiency patients).

In summary, in this Complete Response, the sponsor has addressed each and every safety deficiency appropriately and adequately. The labeling has been revised to reflect all important new safety information. In my opinion, the product can now be considered safe as labeled. In the next section, each major safety deficiency is discussed along with the sponsor's response and the regulatory/scientific outcome.

2.2.1. Drug-Drug Interactions

2.2.1.1. *Nitrates*

In this Complete Response, the sponsor submitted the final study report for a nitrate interaction study. The purpose of the study was not to assess whether tadalafil interacts with nitrates, but rather to assess at what point after dosing with Cialis® the nitrate interaction "wears off". This was considered a critical safety issue to address because of the possible need for nitrate therapy in ED patients during the Cialis® post-dosing period. The protocol design received the Division's concurrence and was also acceptable to the Division of Cardio-Renal Drug Products (DCRDP). In summary, the results revealed that at 24 hours post-dosing with Cialis®, in an average patient, there is still a significant pharmacodynamic (blood pressure) interaction with nitrates. However, at 48 hours post-dosing, by most hemodynamic measures, there is no interaction. Therefore, the sponsor concluded (and the Division concurred) that in the setting where nitroglycerin is required in an average patient who has taken Cialis®, 48 hours should have passed prior to dosing with nitroglycerin and even then, the patient should be carefully monitored. The information from this

trial has been presented in the label in both text and figure format. It appears as a Precaution with clear advice to prescriber and to patient. In addition, the sponsor has proposed means of communicating this risk directly to prescribers and to patients. In my opinion, this constitutes an adequate response to the nitrate deficiency and the issue is fully resolved.

2.2.1.2. Alpha-blockers

In the original NDA, the sponsor had studied the potential interaction of Cialis® with tamsulosin 0.4 mg daily, a highly selective alpha-1a-adrenergic antagonist. The results of this study revealed no clinically significant interaction in terms of additional lowering of blood pressure. This interaction study was conducted to determine the safety of Cialis® therapy in men taking concomitant alpha-blocker therapy for benign prostatic hypertrophy (BPH), since the target populations for both conditions overlap. Based upon this same rationale, the sponsor was asked to conduct a specific drug interaction study with a less selective but widely used alpha-blocker used for treatment of BPH. The Division concurred with the protocol for this study, which included the drug doxazosin at relevant therapeutic dose. The doxazosin study revealed a significant interaction with tadalafil, in terms of additional lowering of the blood pressure. Based upon these results, the sponsor has agreed that use of tadalafil in combination with doxazosin or any other alpha-blocker, other than tamsulosin 0.4 mg daily, is not supported. The current labeling contains a clear statement to this effect in the Contraindications section. In my opinion, this is an adequate response to the alpha-blocker deficiency, and this issue is fully resolved.

2.2.1.3. Alcohol

In the original NDA, the sponsor submitted the results of two interaction studies testing the potential for increased blood-pressure lowering when Cialis was taken in combination with alcohol. One of these studies tested the 10mg dosage strength and another tested the 20mg dosage strength. The clinical review team noted discordance in results between these two trials; specifically, there was no evidence of an interaction in the 20mg study but there was some interaction in the 10mg study. It is reasonable to assume that alcohol will be taken in the same clinical scenario as Cialis, and it is also known that both alcohol and Cialis are vasodilators, therefore resolution of this discrepancy seemed important in demonstrating the overall safety of Cialis. DRUDP requested and the sponsor conducted an additional alcohol interaction study using the 20mg dose. The results of this study revealed a modest increase in blood pressure-lowering and in clinical adverse events when Cialis was taken with 0.7gm/kg of alcohol (equivalent to at least 5 units of alcohol), as compared to when alcohol or Cialis was taken alone. One of the most prominent findings in all three studies was that alcohol itself acts as a potent vasodilator. In comparing the three individual studies, the review team noted that an interaction was seen in both studies that employed the higher dose of alcohol (0.7 gm/kg) as opposed to the study that used the lower dose (0.6 gm/kg). This, we believe, may be the reason that an interaction was seen in both the 10mg study and the second 20mg study but not in the first 20mg trial. Alternatively, there may have been a flaw in the original 20mg study that we have not yet identified. Nevertheless, the clinical review team recommended that there be a clear description of these study results in the label, as well as a Precaution to limit excessive alcohol intake while taking Cialis. Based upon the sponsor's acceptance of this labeling, this issue is satisfactorily resolved.

2.2.1.4. Aspirin/Warfarin

Type 5 phosphodiesterase is found in platelets and drugs that effect this enzyme may impact platelet function. Cialis is a member of the PDE Type 5 inhibitor class. Therefore, for members of this class, it is important to know the clinical effect of drug on bleeding in those patients taking concomitant anticoagulants such as aspirin or warfarin. In the original NDA, the sponsor had conducted these studies only for the 10mg dose but was requesting approval of a 20mg dosage strength. Since a larger dose of Cialis could increase effects on PDE 5 in the human platelet, the Division requested and the sponsor conducted additional 20mg interaction studies between Cialis and warfarin and between Cialis and aspirin. The results of these studies revealed that 1) Cialis did not increase bleeding time changes associated with aspirin and 2) Cialis had no additional effect on prothrombin time or exposure to warfarin in warfarin users. The label clearly describes the results of these studies. Therefore, based upon these results and acceptable labeling, this issue is fully resolved.

2.2.2 Cardiovascular Safety

2.2.2.1 Review of individual cardiovascular adverse events

In the original NDA, there were scattered adverse event reports related to the cardiovascular system including several reports of chest pain, angina pectoris, myocardial infarction, heart failure, arrhythmia, cardiac arrest, syncope, and cerebrovascular accident. Most of these reports were derived from uncontrolled, open-label extension trials. Some of the events occurred during the post-dosing time period following ingestion of Cialis, and therefore, these events could plausibly be related to treatment. Controlled trials did not demonstrate evidence of a drug-related effect on cardiovascular AEs. Therefore, given the lack of clarity in the original review in regard to these AE reports, the Division requested that the sponsor perform a detailed and comprehensive review of the cardiovascular safety of Cialis, to include a qualitative assessment of each of these reports.

The current review of cardiovascular adverse events revealed no evidence to link the open-label cardiovascular AE reports to Cialis. On the contrary, some evidence was provided to support the hypothesis that Cialis has no direct negative effect on cardiovascular function.

First, the clinical review team analyzed narratives for each cardiovascular event occurring in clinical pharmacology trials (25 Cialis events, 1.58%), in controlled clinical trials (60 Cialis events, 1.64%), and in open-label safety trials (87 Cialis events, 4.7%). In the clinical pharmacology and controlled clinical trials, there were no quantitative nor qualitative differences in cardiovascular AE reports between Cialis and placebo. In the open-label trials, there were several reports of death due to cardiac arrest in which a direct link to drug could not be drawn but the relationship remained "possible", in the clinical review team's perspective. This conclusion was repeated following the analysis of such serious adverse events as myocardial infarction, cerebrovascular accident, syncope and hypotension. In summary, these cardiovascular events cannot be directly attributed to Cialis. The reason that causality is so difficult in this situation is that the majority of cases occurred in open-label trials in patients with documented background cardiovascular disease conditions and some events occurred well after dosing with Cialis.

Nevertheless, the sponsor provided the analysis that was requested and cooperated fully in this review. While, causality remains unclear, there is no evidence that Cialis was a direct causative factor in any of these cases. These cardiovascular events are listed in the Adverse Reactions section of the label. Overall, in my opinion, this issue does not pose an impediment to approval and the sponsor's response is acceptable.

2.2.2.2. Cardiac safety trials

During the review of the original NDA, there were two ongoing clinical trials being conducted to assess the cardiac safety of Cialis. One of these, LVBZ, evaluated the effect of Cialis on myocardial perfusion using PET scanning. The other, LVCP, evaluated the effect of Cialis on time to cardiac ischemia in subjects with documented coronary artery disease under conditions of exercise-induced stress. The results of both these studies revealed no cardiac safety risk of Cialis. Cialis caused no decrease in myocardial perfusion when compared to placebo under conditions of stress or while at rest. Further, Cialis caused no decrease in time to exercise-induced myocardial ischemia in subjects with CAD. Therefore, based upon these submissions, this issue is fully resolved.

2.2.2.3. Drug effect on QT interval

For all new molecular entities, an assessment of the effect of the compound on the electrocardiographic Q-T interval is considered appropriate. Although the original NDA contained information relevant to the effect of Cialis on the Q-T interval, it was decided that there was not sufficient information to rule out a clinically meaningful effect. It was especially important to determine the effect of Cialis on QT because of the anticipated widespread use of the compound, the potential clinical risks associated with QT prolongation, and in light of several cardiovascular adverse event reports from open-label trials, including syncope and cardiac arrest. The sponsor designed an appropriate, placebo and positive-controlled trial using doses of Cialis at least 5 times above maximum recommended. These doses effectively covered the "worst-case scenario" with concomitant intake of a metabolic inhibitor of cytochrome P450 3A4. The Division of Cardio-Renal Drug Products approved of the protocol. The results of this trial reveal a minor difference between tadalafil 100mg and placebo of 3.5 millisecond in change-from-baseline of Fridericia-corrected QT interval. While the clinical significance of this difference is not known, our cardiology colleagues commented that no drug with such a small effect on the QT interval has ever been associated with the development of torsades de pointes. Further, the maximum bound of the 95% CI around this mean 3.5 millisecond difference was smaller than 10 milliseconds. These results are documented in Cialis labeling. In my opinion, this issue is fully resolved.

2.2.3 Further investigation of back pain and myalgias

Back pain and myalgias were reported as an adverse event in the original Cialis NDA. In general, these adverse events were reported as mild to moderate in severity and most resolved without treatment. However, in less than 5% of such reports, patients experienced severe pain. Approximately 0.5% of all patients were discontinued for this adverse event. When treatment was required, non-steroidal anti-inflammatory agents were generally sufficient but a small percentage of patients required mild narcotic (e.g. codeine). These events were also reported as lasting up to 12-48 hours and beginning upwards of 12 hours after dosing. While the sponsor recognized all this, they had not conducted an extensive evaluation of the cause of this adverse event, nor proposed adequate labeling. The Division requested a more aggressive search for possible mechanisms but especially to rule out a serious pathophysiologic reason for the AE. The sponsor has since conducted extensive and detailed examinations of back pain/myalgias in over 140 patients who underwent a prospectively defined "algorithm" of diagnostic tests. In addition, the sponsor conducted a clinical study using radionuclide scans to evaluate the effect of Cialis on blood flow to the kidney, back and gluteal muscles in volunteers. The results of all these studies revealed no medically serious pathophysiologic reason for the pain. The radionuclide

scans revealed no effect of Cialis on renal blood flow and only *increased* blood flow to the large muscles of the back and gluteals. The extensive "algorithm" protocol, conducted in over 140 patients with the adverse event, revealed no evidence of systemic inflammation, no rhabdomyolysis, no immunological phenomenon, and no changes in clinical laboratories of any sort. Based upon this extensive evaluation of the problem with assurance that no serious underlying pathology has been found, and a clear description of this AE in the product label, the issue is no longer an impediment to approval. It appears to pose a tolerability issue only. From a regulatory standpoint, this issue is resolved.

2.2.4 Safety in Special Populations

2.2.4.1. Patients with diabetes mellitus

In the original NDA, the Division requested additional information that Cialis was studied in men with diabetes mellitus, an important subgroup of men with ED, both in terms of efficacy and safety considerations. The Division was concerned that the total number of diabetics in the trials was too small and that they were pre-screened and excluded for baseline orthostasis. In this Complete Response, the sponsor has convincingly demonstrated that sufficient numbers of diabetics have been studied, that the pre-screening actually excluded not a single diabetic patient, and that the efficacy and safety of the compound in this important subgroup was confirmed. For example, over 700 diabetics have received tadalafil and over 215 diabetics have received the 20mg dose. The adverse event profile for Cialis is no different in diabetics than in non-diabetics. There are no additional serious events noted. Thus, this issue is fully resolved.

2.2.4.2. Patients with renal insufficiency

In the original NDA, it was noted in one Phase 1 pharmacokinetic study that patients with moderate degrees of renal insufficiency demonstrated an increased incidence of back pain and myalgia at the 10mg dosage strength. Overall exposure in these patients was increased approximately 2-fold compared to patients without renal insufficiency. Renal insufficiency had its greatest impact on clearance of the compound with subsequent increases in elimination half-life. The Division sought clarification in regard to the appropriate dose in this population, as well as in those with severe renal insufficiency (including patients on dialysis). In the Complete Response, discussions with the sponsor have led to the introduction of a 5mg dose - to be used as a starting dose in those patients with moderate renal insufficiency, and as the only dose in patients on dialysis. In those with moderate insufficiency renal insufficiency, the 5mg dose may be used once daily and a maximum dose of 10mg may be taken no more than once every 48 hours. Based upon the demonstrated safety of the 5mg dose in these patients and pharmacokinetic appropriateness of this regimen, these solutions are acceptable. Thus, this issue is fully resolved.

2.3. Chemistry, manufacturing and controls (CMC)

In the original NDA, there was an outstanding chemistry issue. Specifically, the site of manufacture of the drug product in Indianapolis, Indiana was "on withhold" by the Office of Compliance due to cGMP violations. This posed an approvable deficiency. The sponsor has since withdrawn this site from the request and has subsequently demonstrated the ability to manufacture the product at an alternate location in Puerto Rico. The site in Puerto Rico is cGMP compliant. And, the lowest dose, 5mg, can also be manufactured within specifications at the

Puerto Rico site. Therefore, based upon the acceptability of this NDA to our chemistry section and to the Office of Compliance, this issue is resolved.

3. Relevant issues from other disciplines and consultants

3.1. Division of Cardio-Renal Drug Products (DCRDP)

The Division of Cardio-Renal Drug Products was asked to review the results of the ritonavir-tadalafil interaction study (LVEV) and the thorough QT study (LVFB). In their finalized review, dated 3- July-2003, Drs. Stockbridge and Throckmorton concluded the following:

“Study LVFB was conducted with a dose of tadalafil producing plasma levels higher than usually achieved with the highest recommended dose, 20mg, coupled with 3A4 inhibition. Study LVFB was able to detect *incontrovertible* evidence of a small effect on repolarization, 3 to 6 msec, with no outliers. What mortal risk does this level of QT prolongation represent? While it is not possible to exclude risk associated with small effects on repolarization, there are no known examples of manifest risk associated with drugs that produce an effect of this magnitude. Any risk there may be is apt to be no greater than for other risks implicit in a clinical experience of the present size.”

Thus, this thorough QT Study, LVFB, provides direct evidence that tadalafil has a minimal effect on the Q-T interval that is not likely to be associated with adverse clinical outcomes.

3.2. Division of Anti-Inflammatory, Analgesic and Ophthalmological Drug Products (DAAODP)

The Division of Anti-Inflammatory, Analgesic and Ophthalmological Drug Products (DAAODP) were asked to review the results of three controlled clinical studies conducted to assess the effects of Cialis on vision (Studies LVFF, LVAN and LVCN). In his finalized review, dated 9-October-2003, Dr. Chambers concludes:

“From an ophthalmological perspective, there is no objection to the approval of this NDA provided that the labeling is consistent with other phosphodiesterase inhibitors.”

He also comments:

“Additional adequate and well-controlled studies are recommended to better quantitate the effect of tadalafil on color vision and retinal physiology (as measured by ERG testing). In particular testing after repeat dosing should be performed.”

In summarizing his reasons for this decision, Dr. Chambers believes that the 3 studies testing the effect of Cialis on vision were flawed in their conduct. Study LVFF was flawed by failure to evaluate eyes independently in the Farnsworth-Munsell test (as opposed to the binocular testing that was done). Study LVAN was flawed by: 1) repeated failure to properly conduct Farnsworth-Munsell testing, 2) failure to conduct some scheduled electroretinograms [ERGs], and 3) inconsistent and unlikely scores on visual acuity testing. Study LVCN was flawed by: 1) failure to analyze the results of the Farnsworth-Munsell test according to the protocol, 2) failure to document some numerical test results where these results were available, and 3) failure to demonstrate that the positive control had positive findings. Nevertheless, for study LVFF, it was

noted that there was no effect of Cialis on visual acuity compared to placebo and that the results of electroretinogram testing *did* reveal an independent effect of Cialis.

In terms of ocular adverse events, the original NDA contained reports of 3 patients who reported color vision changes (blue vision), while the Complete Response contained none. The current post-marketing adverse events database revealed 10 reported ocular AE reports including: conjunctivitis, eye redness, vision blurred, eye pain, eyelid edema, and eye pruritis. These terms are consistent with previous reports in the original NDA.

In sum, Dr. Chambers felt that minimal information could be derived from the 3 vision studies. He also felt that the clinical experience was not unlike the previous PDE5 inhibitors. Therefore, he recommended that the label should describe only those findings for which there is adequate support and otherwise should be no different than the other PDE5 inhibitors. The Division translated this guidance into the label and the sponsor ultimately agreed to accept "class" labeling for effects on vision. A Phase 4 commitment has been obtained to conduct an additional clinical trial with the objective of investigating the effect of Cialis on color vision and retinal physiology (by electroretinogram) following multiple doses of Cialis or placebo.

3.3. Biometrics

In his finalized memo, Dr. Welch notes that there are only three statistical issues in the Complete Response that require his comment: 1) applicability of data to the U.S. population, 2) claims pertaining to duration of effectiveness, and 3) starting dose.

In regard to *applicability to the U.S. population*, Dr. Welch reviewed the two new Phase 3 U.S. trials LVCR and LVEF. He concluded: "The efficacy results for the U.S. studies are consistent with the results of the original studies." In addition, Dr. Welch notes that the sponsor conducted subgroup analysis in those patients of African-descent versus non-African descent patients and Hispanic and non-Hispanic patients. While the numbers of patients in these analyses were too small for formal claims, the efficacy results were similar across groups.

In regard to _____, Dr. Welch reviewed studies LVCK, LVDG and LVFD. In regard to the _____ trial LVCK, Dr. Welch concluded: "For study LVCK, labeling could include a descriptive summary of the percentages of patients, by treatment group, who had at least one successful attempt (out of four) within 30 minutes of dosing. The label has been revised accordingly. In regard to Study LVDG, Dr. Welch concluded: "For Study LVDG, labeling discussion could include presentation of the primary efficacy measure, the percentage of successful attempts at _____ after dosing; any such table should also show the number of patients. A more meaningful presentation might be the percentages of patients who had least one successful event. As noted in the original statistical review, labeling should not include any reference to _____. Again, labeling has been revised accordingly. Finally, Dr. Welch conducted a review of new study LVFD. He found the protocol for LVFD and its statistical analyses to be satisfactory. The results for the mean percent of successful attempts ("yes" to Question #3 of the SEP diary) at _____ hours was 42%, 56% and 67% for placebo, 10mg and 20mg groups, respectively. At _____ hours the results for placebo, 10mg and 20mg were 33%, 56% and 62%, respectively. The differences between tadalafil and placebo were statistically significant at both timepoints. Dr. Welch concluded: "This reviewer has no objection to including these primary results in the proposed label." Again, the label describes these results as recommended here.

In regard to *starting dose*, Dr. Welch does not accept the sponsor's arguments that 20mg is an appropriate starting dose based upon pooled (and exploratory) efficacy analyses. The clinical team agrees from both an efficacy perspective and a clinical tolerability perspective. The sponsor has agreed to a starting dose of 10mg with either up- or down-titration as appropriate for each patient.

Therefore, based upon this review, all statistical issues are resolved.

3.4. Pharmacology and toxicology

In their final memo for this Complete Response, Drs. Thornton and Shin still agree with the original Pharmacology/Toxicology recommendation of approval. Dr. Shin does, however, comment:

“The etiology and/or mechanism of myalgia and back pain observed in humans associated with Cialis are not clearly understood.”

Reviewer's comment: I agree with Dr. Shin's conclusion.

In her 6-page memo, there are three major items reviewed: 1) the effect of tadalafil on PDE11A1, 2) the effect of tadalafil on the human cardiac I_{Kr} current, and 3) back pain and myalgias.

In regard to PDE11A1, an additional PDE assay was submitted that confirmed the results of prior assays. The sponsor tested the parent and three metabolites. Dr. Shin concluded that based upon the “PDE11A1 to PDE5A1 ratio”, tadalafil and its metabolites were “highly selective” for PDE11A1, and that Cialis or its catechol metabolite “may alter the activity of PDE11A1 at therapeutic doses”. Dr. Shin further commented that PDE11A1 has been found “mainly” in human skeletal muscle (and also in liver, testes, kidney, pituitary, thyroid and salivary gland) and that physiological roles and clinical consequences of PDE11A1 inhibition have not been elucidated. Finally, her draft review states: “Although the physiological significance and its clinical consequences of PDE11A1 inhibition have not been elucidated, the inhibition by Cialis and/or its catechol metabolite on PDE11A1 at therapeutic doses could lead to an increase in certain adverse effects such as musculoskeletal disorders”

Reviewer's comment: Dr. Shin's comments are acknowledged. The effect of Cialis on PDE11A1 has been included in the label, accompanied by the following statement: “The physiological role and consequence of PDE11 inhibition in humans have not been defined.” Our pharmacology review team (including Dr. Shin) and the sponsor accepted this labeling. However, in my view, the linkage of back pain and myalgias to inhibition of PDE11A1 requires remains speculative. The large body of clinical evidence collected in regard to back pain and myalgias reveals no evidence of striated muscle damage (no increases in CPK, no rhabdomyolysis), and no cases of death, serious outcome, or disability due to myalgia or back pain in over 7000 patients treated in controlled trials and thousands more already receiving approved drug outside the U.S. All reports of back pain or myalgia have resolved spontaneously. While I acknowledge Dr. Shin's concern regarding the tadalafil and catechol metabolite effect on PDE11A1, I do not believe that this finding should preclude approval nor can it be clearly linked to the back pain and myalgias. Nevertheless, the label has been revised to present accurate information in regard to the effect of Cialis on PDE11A1 and in regard to the clinical symptoms of back pain/myalgia. Further, to support my overall position, there have been

no signals of serious disease or clinical consequences derived from extensive human safety information collected in regard to back pain/myalgias.

In regard to the hERG study (Ikr), all three PDE5 inhibitors that were tested reduced the hERG current amplitude in a dose-dependent manner. Accurate dose-response information could not be gathered for tadalafil because of inability to place enough tadalafil into solution for purposes of the experiment. Nevertheless, the IC50 for hERG blockade occurred only at parent concentrations of approximately 127-fold times than therapeutic dose concentrations, thus demonstrating that “the drug has a weak evidence of QT prolongation risk”.

Reviewer’s comment: The thorough QT study in humans revealed no evidence of clinical concern.

In regard to back pain and myalgias, Dr. Shin reviewed both the pre-clinical findings and the human reports and studies. She described the nature of the symptoms in humans and the overall lack of significant pathophysiologic findings. For example, there were no changes in serum erythrocyte sedimentation rate (ESR) nor in serum creatinine phosphokinase (CPK) in over 150 patients who complained of back pain and myalgias. Also negative were serum aldolase, urine hemoglobin, serum transaminases, C-reactive protein, and percentage of eosinophils. Nor was there any dose-related increase in ESR or CPK in trials when these biomarkers were collected in controlled studies. Dr. Shin also reviewed the results of the retrospective and prospective human analyses (for back pain/myalgias). She also reviewed the results of the ritonavir interaction study, (where parent drug levels were maximized); and the study in end-stage renal disease patients, (where metabolite concentrations were maximized). Neither study was indicative of worsened back pain or myalgias. She acknowledges no signs of rash, fever, hematuria or any other overt clinical evidence of immunological phenomenon in the entire NDA.

Nevertheless, Dr. Shin remains concerned that the back pains and myalgias could represent initial symptoms of “*hypersensitivity vasculitis*”. In this regard, she makes the following points:

1. Vasculitic manifestations of hydralazine have been seen at 6 months to 13 years after initiating treatment with hydralazine and these manifestations were preceded by arthralgias and myalgias.
2. The catechol metabolite of Cialis may act as a possible mediator of this potential “hypersensitivity vasculitis”. Dr. Shin states that it may act as an “immunogenic epitope of drug-hapten formation”. She presents methyldopa and levodopa as two drugs with catechol moieties that have been associated with hypersensitivity reactions.
3. Tadalafil produced disseminated arteritis (not just cardiac lesions) in dogs with the Beagle Pain Syndrome in the 1 and 6-month studies in the absence of hemodynamic changes. This was not confirmed in a 1-year dog study in dogs without the Beagle Pain Syndrome. However, two dogs in the “clean” 1-year study still had “marked thrombocytopenia and neutropenia at 14-18 fold human exposures”. Dr. Shin comments that these findings may be “indicative of immune-mediated effects”.
- 4.

Ultimately, Dr. Shin believes that the current information is not sufficient to rule out drug-induced vasculitis because [verbatim]:

1. "Limited information on preclinical/clinical findings is available because of poor understanding of pathogenesis to assess risks to humans";
2. "There is a lack of valid markers for nonclinical and clinical monitoring";
3. "Cialis is different from sildenafil and vardenafil with a distinct chemical structure and a longer duration of action";
4. "Cialis is metabolized to catechol, methylcatechol and then to methylcatechol glucuronide, which possess a catechol moiety responsible for certain drug-induced hypersensitivity."; and
5. "Cialis and/or its catechol metabolite possess unknown physiological roles due to PDE11A1 inhibition within therapeutic range with a 5-14 fold selectivity (PDE11A1 vs. PDE5A1) compared to Viagra and Levitra with a >300-fold selectivity."

In her formal Toxicology Team leader's review, Dr. Thornton summarizes:

"Regardless of Dr. Shin's concerns, she and I support her previous recommendation of 'approval' for the NDA. Appropriate labeling revisions including the addition of PDE11 information and the addition of an "Animal Toxicology" section detailing the non-clinical arteritis findings has been included and accepted by the sponsor", and

"The pharmacology and toxicology data supports approval of this NDA. There are no outstanding issues"

In a formal eMAIL to the Division, John Leighton, Supervisory Toxicologist at CDER concurred.

Reviewer's comments: I agree with Dr. Shin that the actual pathogenesis for the back pain and myalgia has not been elucidated. This has been made clear in the label. I also acknowledge her excellent reviews of the pre-clinical and selected clinical data and in fact, much of this data has been presented in the label. Like our toxicology team, I do not find the concerns regarding back pain and myalgia to be sufficient reason to take a not approval action. There is evidence from 7000 subjects in clinical trials that Cialis is safe. There has been an aggressive and comprehensive clinical work-up of the clinical symptoms: back pain and myalgia. Valid markers of inflammation and/or muscle breakdown have proven negative in over 150 patients who have actively complained of the condition. The condition has resolved in all patients who have experienced it. It has led to no deaths, no SAEs, and perhaps one or two medically significant episodes of pain. There has been no evidence of any type of hypersensitivity reaction in this entire NDA, or in the post-marketing period in Europe. Finally, I find some of Dr. Shin's comments to be speculative and to lack substantial evidence, including the following:

- 1) intimating a linkage between disseminated arteritis in dogs with Beagle Pain Syndrome (in the 1 and 6-month studies) to back pain/myalgias in humans, and

- 2) inferring that the catechol metabolite(s) may act as an immunologic hapten which induces antibody formation and allergic reaction.
- In my opinion, there is simply no direct clinical evidence to support these hypotheses for back pain and myalgias with Cialis.

3.5. Clinical Pharmacology and Biopharmaceutics (OCPB)

In her final memo, Dr. Kenna notes:

“The resubmission of NDA 21368 for tadalafil tablets is acceptable from the Clinical Pharmacology and Biopharmaceutics perspective.”

The sponsor has agreed with marketing a 5mg dose and has supplied all necessary information for its approval. The sponsor has also incorporated all of the OCPB labeling revisions. In my discussions with Dr. Kenna and in her final review, she found the application to be acceptable.

In her current review, Dr. Kenna focused on 5 studies as follows:

- 1) the pharmacokinetic study in men on hemodialysis for renal failure,
- 2) the ritonavir and ketoconazole drug interaction study,
- 3) the thorough QT study
- 4) the drug interaction study with doxazosin, and
- 5) an in-vitro study of the effect of tadalafil on CYP 2C19

In regard to the use of tadalafil in those *patients with renal insufficiency (including those on hemodialysis)*, OCPB concluded that a 5mg dose (maximum use of once daily) is appropriate for patients with end-stage renal disease on dialysis and for patients with moderate renal insufficiency. In these groups, a 10mg dose may be taken but only at a maximum frequency of once every two days. The reason for this dose adjustment is that in those patients with moderate renal insufficiency, there is a 1.2-fold increase in C_{max} and a 1.7 to 2.1-fold increase in AUC compared to normal volunteers. Also, back pain was increased in incidence in this group at the 10mg dose compared to the 5mg dose. In those patients with end-stage renal disease (ESRD) the corresponding increases in C_{max} and AUC are 0 to 1.9-fold and 1.1 to 2.7-fold, respectively. The sponsor has agreed to this dosing paradigm. Based upon clinical evidence of safety for the 5mg dose in these populations and the agreed-upon dose adjustments, this issue is considered resolved.

In regard to the *ritonavir and ketoconazole interaction study*, once daily administration of ketoconazole caused the maximum increase in tadalafil levels; specifically, 1.2-fold increase in C_{max} and 4.1-fold increase in AUC. The increase with ritonavir was lower. Therefore, dosing in patients has been adjusted so that the label recommends a maximum dose of 10mg not to exceed once every three days. This issue is considered resolved.

In regard to the *thorough QT study* OCPB agrees with Cardio-Renal Division that the design and conduct of the study were appropriate and that the results revealed only a small (3-5 millisecond) increase from baseline in QTc compared to placebo, at doses that exceeded the worst-case scenario for metabolic inhibition.

In regard to the *doxazosin* study, OCPB and Clinical have agreed that there was a clinically significant effect on blood pressure when doxazosin was administered with tadalafil compared to when tadalafil was administered alone. Dr. Kenna's review describes the results of this

randomized, double-blinded, placebo-controlled crossover trial in 18 healthy middle-aged men taking doxazosin 8mg. There were statistically and clinically significant differences in mean maximal post-baseline drops in standing systolic BP and standing diastolic BP and maximal increases in standing pulse rate. For the combination group, the mean maximal drops in standing systolic and diastolic BP were 27.8 mm Hg and 14.4 mm Hg versus corresponding drops of 17.9 mm Hg and 9.11 mm Hg for doxazosin alone. For pulse rate the mean maximal changes from baseline were +16 bpm for the combination versus +12.3 bpm for doxazosin alone. Additional data from other endpoints confirmed this finding. Therefore, based upon this finding but the finding in our previous reviews of no significant interaction with tamsulosin 0.4mg daily, there is a Contraindication for the use of tadalafil with any alpha-blocker other than tamsulosin 0.4mg daily.

[_____

_____]

[_____

_____]
[_____]

Finally, Ms. Best and Piazza-Hepp from DSRCS provided the Division with their comments on the proposed Patient Information leaflet. These were taken into consideration and incorporated into the approved PPI. All issues related to risk communication labeling to patient are considered resolved.

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mark S..Hirsch
11/20/03 10:33:28 AM
MEDICAL OFFICER

Daniel A. Shames
11/20/03 01:46:53 PM
MEDICAL OFFICER

Lilly ICOS LLC
c/o
Lilly Research Laboratories
A Division of Eli Lilly and Company

Lilly Corporate Center
Indianapolis, Indiana 46285

November 19, 2003

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
5600 Fishers Lane
Rockville, Maryland 20857

**NDA Amendment:
Documentation of
Phase 4 Commitment**

Re: NDA 21-368, IC351; Documentation of Phase 4 Commitment

Reference is made to NDA 21-368 submitted on June 28, 2001 and to recent telephone conversations between representatives of DRUDP and Lilly ICOS. In those conversations, agreement was reached regarding a phase 4 commitment for NDA 21-368. The agreement is specified below.

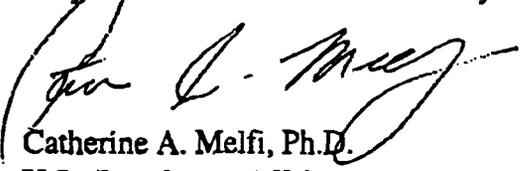
Lilly ICOS agrees to the following phase 4 commitment:

To conduct a randomized, placebo-controlled study investigating the effects of Cialis on color vision and retinal physiology (electrorétinography) following multiple daily doses. The timeline is as follows:

Protocol Submission	within 3 months
Study Initiation	within 10 months
Final Report Submission	within 18 months

Please call me at (317) 277-2905 or Susan Sullivan at (425) 415-5649 if there are any questions. You may also call Elizabeth Bearby at (317) 276-1203.

Sincerely,
Lilly Research Laboratories for Lilly ICOS LLC



Catherine A. Melfi, Ph.D.
U.S. Regulatory Affairs

Mercier, Jennifer L

From: Collier, Bronwyn E
Sent: Wednesday, November 19, 2003 12:04 PM
To: Houn, Florence; Beitz, Julie G; Kober, Margaret; Mercier, Jennifer L; Kim, John; Shames, Daniel A; Hirsch, Mark S; Griebel, Donna J
Subject: FW: Cialis action update

-----Original Message-----

From: Leighton, John K
Sent: Wednesday, November 19, 2003 11:13 AM
To: Collier, Bronwyn E
Subject: RE: Cialis action update

The division has addressed all the issues raised in my original memo. There are no issues from pharm tox.

-----Original Message-----

From: Collier, Bronwyn E
Sent: Tuesday, November 18, 2003 1:26 PM
To: Duffy, Eric P; Leighton, John K
Cc: Mercier, Jennifer L
Subject: Cialis action update

Things are moving along on Cialis and action (approval is anticipated this Friday). Please let me know if you need anything besides the materials sent.

Thanks,
Bronwyn